REMARKS

Applicants respectfully request reconsideration of the present application in view of the following reasons.

I. Disposition of the Claims

Claims 1-10 are pending and stand rejected. Claims 11-18 are canceled without prejudice or disclaimer.

II. General Comments

A. Foreign Priority

The claim for foreign priority of record was not acknowledged of record. The present application has claimed the benefit of application, Japan no. 133524-1993, filed June 7, 1993. See Declaration from the Broadening Reissue, page 2, paragraph 5, top; original ADS dated February 19, 2004, page 3.

The reference to Japan no. 133524-1993 should be replaced with Japan no. 135524-1993. This error was an inadvertent typographical error. Indeed, the claim for priority appears on page 1 of the application as filed:

(30) **Foreign Application Priority Data**

Jun. 7, 1993 (JP) 5-135524

In addition, this paper is accompanied by the following:

An unsigned supplemental declaration (to be returned when all signatures are gathered);

A supplemental ADS; and

a request for a corrected official filing receipt.

It is respectfully requested that the claim for priority be acknowledged. It is believed that the certified copies of the priority documents are in a family member application.

B. Claims 11-18

Form PTOL-326 indicated that claims 11-18 were withdrawn. It is believed that these claims were examined as they were rejected. Office action, p. 2. Thus, this paper responds as if these claims were rejected and thus of record.

Since claims 11-18 are canceled without prejudice or disclaimer, as to these claims, each rejection should be withdrawn.

C. Claim Amendments of May 31, 2005

The Examiner is thanked for noting that the amendments should comply with Rule 173(b). Office action, p. 3. The Examiner is also thanked for entering the amendment of May 31, 2005.

D. Interview

The Examiner is thanked for granting the interview dated January 30, 2006. The substance of the interview is reflected in these remarks.

E. Present Claim Amendments

Claims 1, 4, and 7 are amended. The current amendment of claim 1 removed the extra unmatched bracket "methyl]]" and returned the paragraph structure to its original form. This error and its solution is believed obvious from the face of the patent that made this Reissue Application. The amendment of claim 4 removed the extra space in "methy l" and gave the paragraphs a format analogous to that of claim 1. The current amendment of claim 7 gave the paragraphs a format analogous to that of claim 1. No new matter has been added.

Applicants respectfully request that this Amendment under 37 C.F.R. § 1.116 be entered by the Examiner, placing each claim in condition for allowance. Applicants submit that the proposed amendments of each presently amended claim do not raise any new issues or necessitate the undertaking of any additional search of the art by the Examiner, since all of the elements and their relationships claimed were either earlier claimed or inherent in the

claims as examined. Therefore, this Amendment should allow for immediate action by the Examiner.

Finally, it is submitted that the entry of the amendment would place the application in better form for appeal, should the Examiner dispute the patentability of the pending claims.

In view of the foregoing remarks, Applicants submit that this claimed invention, as amended, is neither anticipated nor rendered obvious in view of the references cited against this application. Applicants therefore request the entry of this Amendment, the Examiner's reconsideration and reexamination of the application, and the timely allowance of the pending claims.

III. The PTO Failed to Distinguish the Teaching of the Prior Art from the Teaching of the Specification

The present combination of enablement and obviousness rejections is based on a failure to distinguish the teaching of the prior art from the teaching of the specification. As explained by SPE Y. Eyler in her talk to the Biotech Customers on October 29, 2003 (a copy of "*The Squeeze: Art and Enablement Together*," is attached for consideration), the improper squeeze creates a catch 22 dilemma for an applicant; a scenario that makes it impossible to argue the patentability of the rejected claims. As a result, she explained that combining § 112, 1st paragraph, and § 103(a) rejections is improper when an application discloses more than the reference(s) used in the § 103(a) rejection.

Such is the case here, making the present § 112, 1st paragraph, and § 103(a) rejections improper. Indeed, the present specification contains multiple working examples. On the other hand, the references used in the § 103(a) rejection do not. Clearly, the present rejections are a paradigm example of the improper squeeze, and they must be withdrawn.

Additional comments follow below. But each rejection should be withdrawn for the reason above.

A. Diuretic and Calcium Antagonist Combinations

Claims 4 and 7 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement for "all and any compound having diuretic or calcium antagonistic activity." Office action, p. 2 (quoted language from the previous action). Of record, the PTO explained that the present examples using HCT and MDP do not reasonably provide enablement for all combinations such that the person of skill in the art would be unduly burdened to practice the invention as claimed.

Yet, in the same record, the PTO urged that a hypothesis in Chakravarty (EP 0 400 835 A1) rendered obvious any and all combinations of both benzimidazoles and either a diuretic or a calcium channel blocker, regardless of whether or not the benzimidazole is described by Chakavarty. The PTO's position is self contradictory, because the facts alleged to support the § 112, 1st paragraph rejection and the facts alleged to support the § 103(a) rejection cannot both be true at the same time. That certainly means that the PTO's rejection cannot stand for lack of substantial evidence and explanation. Applicants therefore respectfully request that the PTO reconsider and withdraw the rejection.

Moreover, there is no evidence and explanation of record explaining why, at the time of invention, one of ordinary skill in the art, guided by the present specification, could not select a *compound having diuretic activity* and/or a *compound having calcium antagonistic activity*. Indeed, the terms "diuretic" and "calcium channel blocker" are used in Chakravarty. Similarly, the terms "diuretic" and "calcium antagonist" are used in Cardiovascular Pharmacology, pp. 257-61, 415-16 (Michael J. Antonaccio, PhD, Ed., Raven Press New York 1984) (enclosed for consideration). Thus, it is submitted that a *compound having diuretic activity* and/or a *compound having calcium antagonistic activity* could have been identified as of the present application's ultimate parent's filing date.

Additionally, there is no evidence and explanation of record explaining why, at the time of invention, one of ordinary skill in the art, guided by the present specification, could not then determine the efficacy of a given composition against a particular *angiotensin-II*

mediated disease other than by those explicitly recited in the specification and why such routine determining would amount to undue experimentation.

The PTO's position about "essentially reaching through into the future to include compounds yet to be discovered" (Office action of 11-30-2004, p. 3) is similar to the position that was flatly scorned in *In re Hogan*, 559 F.2d 595, 194 USPQ 527 (CCPA 1977) (enclosed for consideration). In *Hogan*, the PTO rejected claims for lack of enablement after concluding that, in light of post-application developments (after-arising technology), the claims were broad enough to embrace certain after-arising embodiments that were not enabled by the application. *Hogan,* at 536-37. The Court of Customs and Patent Appeals reversed the PTO, holding that it was enough that the application enabled the claims as construed in light of the state of the art at the time of filing. *Hogan,* at 537. As the court explained, "[t]he use of a subsequently-existing improvement to show lack of enablement in an earlier-filed application on the basic invention would preclude issuance of a patent to the inventor of the thing improved, and in the case of issued patents, would invalidate all claims ... therein." *Hogan* at 538.

In the present case, the PTO attempts the revive the PTO's position in *Hogan*, which the predecessor to the Federal Circuit decided was improper. This attempt is most certainly as improper now as it was at the time of *Hogan*, and the rejections should be withdrawn.

B. Rejection of Claims Under 35 U.S.C. § 103(a)

Claims 1-10 were rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over EP 0 459 136 A1 to Naka *et al.* ("Naka") in view of Chakravarty. Office action, p. 3. As already noted, the PTO's position is self contradictory, because the facts alleged to support the § 112, 1st paragraph rejection and the facts alleged to support the § 103(a) rejection cannot both be true at the same time. That means that the PTO's rejection cannot stand for lack of substantial evidence and explanation. Applicants therefore respectfully request the PTO to reconsider and withdraw the rejection.

C. 35 U.S.C. § 112, first paragraph, Angiotensin-II Mediated Diseases

Claims 1 and 4-7 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement for the entire scope of claimed angiotensin-II mediated diseases. Office action, pp. 2-3. In the previous action, the PTO added that methods pertaining to only some diseases, such as hypertension and other circulatory diseases, are enabled. In the present case, the Examiner suggested enumerating the "actual diseases contemplated by [the] mechanism" to traverse the rejection. Office action, p. 3. Although the Examiner is thanked for the suggested language to avoid the rejection (p. 3), the suggestion is not adopted.

As an initial matter, the rejection of composition claims 4-6 is improper, because the specification offers extensive teachings on the compositions *per se*. *See* the '481 patent at col. 10, l. 62 - col. 14, l. 35. In any event, claims 4-6 do not recite an angiotensin-II mediated disease. As to these claims, the rejection should be withdrawn.

As relevant to the other rejected claims, the rejection reasoned that the PTO's position on "mechanism claims" has changed since the parent application was filed. Office action, p. 2. Yet there are no *per se* rules about enablement:

> The examiner must then weigh all the evidence before him or her, including the specification and any new evidence supplied by applicant with the evidence and/or sound scientific reasoning previously presented in the rejection and decide whether the claimed invention is enabled. The examiner should never make the determination based on personal opinion.

MPEP § 2164.05. "The determination should always be based on the weight of all the evidence." MPEP § 2164.05. Thus, when the PTO applied a *per se* policy regarding "mechanism claims," Office action, p. 2, use of that *per se* policy must be on its face improper.

Enablement is judged not only on a case by case basis but also as of the time of the invention. There is no evidence and explanation of record explaining why, at the time of invention, one of ordinary skill in the art, guided by the present specification, could not screen the efficacy of a given composition against a particular *angiotensin-II mediated disease* other

than by those explicitly recited in the specification and why such screening would amount to undue experimentation. Applicants, therefore, request that the PTO reconsider and withdraw this ground for rejection.

The present case is not one in which Applicants claim, for the first time, that they discovered an *angiotensin-II* receptor, and then Applicants claim any disease modulated by that receptor. To the contrary, the renin-angiotensin-aldosterone (RAA) pathway was shown to involve *angiotensin-II* in a review article at least as of June 6, 1994. *See* review article by R.J. Cody, 47 Drugs 586-98 (April 1994) ("Cody," enclosed for consideration) (see, e.g., pp. 587-et seq.). *Angiotensin-II*, according to Chakravarty, is produced in the blood by ACE:

> failure. Angiotensin II (AII), an octapeptide hormone is produced mainly in the blood during the cleavage of angiotensin I by angiotensin converting enzyme (ACE) localized on the endothelium of blood vessels of lung, kidney, and many other organs, and is the end product of the RAS AII is a powerful arterial vasoconstricter that exerts its action by interacting with specific receptors present on cell membranes. One

Chakravarty, p. 3. (See, also, ACE has been identified in blood vessel walls. Cody, *supra.*, p. 587, col. 2). Cody's Figure 1 notes, in cartoon fashion, the relationship between *angiotensin II* receptors and the adrenal gland, vascular, myocardial, brain, and other sites.

Along these lines, peptide antagonists of *angiotensin-II* were studied. Cody, *supra.*, pp. 593-et seq. And examples of *angiotensin-II mediated diseases* were known. Cody, *supra.*, pp. 589, col. 1 (see, e.g., 589, col. 2, p. 590, col. 1) (see also "The dependence of vascular tone on angiotensin-mediated vasoconstriction can be identified in both animal models and clinical studies and the intensity of this effect can be modulated by the sodium status.") (emphasis added). Clearly, the *angiotensin-II* receptors were known and antagonists thereof were investigated.

On top of this knowledge, the present specification as filed lists exemplary diseases:

> is also made of a mixture of them or a combination of them.
>
> The angiotensin II mediated diseases include hypertension, cardiac insufficiency, ischemic peripheral circulation disturbances, myocardial ischemia, vein insufficiency, progressive cardiac insufficiency after myocardial infarction, diabetic nephritides, nephritis, arteriosclerosis,. hyperaldosteronism, dermatosclerosis, glomerulosclerosis, renal insufficiency, diseases of central nervous system, sensory disturbances including Alzheimer's disease, deficiency of memory, depression, amnesia and senile dementia, anxiety neurosis, catatonia or indisposition, glaucoma, intraocular high tension.

Present specification, col. 10. It contains examples. Present specification, cols. 14-17. Clearly, the weight of all the evidence points toward the enablement, beyond the diseases just listed, of the presently rejected claimed invention, and the rejections should be withdrawn.

IV. Rejection of Claims Under 35 U.S.C. § 112, Second Paragraph

Claims 1-10 were rejected 35 U.S.C. § 112, second paragraph, as being allegedly indefinite for reciting the term "mediated," which, in the PTO's analysis, ambiguously refers to a direct or an indirect mechanism. Office action, p. 3 (noting comments of the previous Office action too). Applicants respectfully traverse the rejection.

The second paragraph of Section 112 requires only that the claim reasonably apprise those skilled in the art of the scope of the claimed invention. See, e.g., *Miles Lab, Inc. v. Shandon, Inc.*, 27 U.S.P.Q.2d 1123 (Fed. Cir. 1993), *cert. denied*, 510 U.S. 1100 (1994); see generally MPEP § 2171. Specifically, the definiteness of claim language must be analyzed in light of (1) the entire content of the particular specification, (2) the teachings of the prior art, and (3) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. See MPEP § 2173.02. Applicants maintain that the claims would have reasonably apprised those skilled in the art of the scope of each presently rejected claimed invention.

The PTO stated that the claims must be interpreted in light of the specification. Applicants agree and add that 35 U.S.C. § 112, first paragraph requires that the specification contain a written description of any claimed invention. Because each and every presently rejected claimed invention is fully supported by an enabling, written description, there exists evidence of guidance for one skilled in the art to be reasonably apprised of each presently rejected claimed invention.

Additionally, the specification concludes with claims, as is explicitly clear from the statute used by the Office for support of the present rejection, 35 U.S.C. § 112, second paragraph ("The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards has his invention.").

As a result, the entire specification, including the claims (as originally filed), must be consulted to determine definiteness. So, the claims as originally filed must be consulted to determine definiteness, because these claims are part of the specification.

Moreover, the present specification contains multiple working examples. These examples, being part of the present specification, must be consulted to determine definiteness. Collectively, the written description, the claims as filed, and the examples provide ample evidence of guidance for one skilled in the art to be reasonably apprised of each presently rejected claimed invention.

Furthermore, it is realized that the Office is supposed to give each claim its broadest reasonable interpretation. See MPEP § 2111. Applicants respectfully submit, however, that the breadth of a claim is not to be equated with indefiniteness. See MPEP § 2173.04; *see also In re Miller*, 441 F.2d 689, 169 U.S.P.Q. 597 (C.C.P.A. 1971). Examination focuses upon whether the claims convey a reasonable degree of clarity and precision, not whether the claims are broad. See MPEP § 2173. The reasonable degree of clarity and precision would be absent if the broadest reasonable interpretation could have an indiscernible meaning. Such an unknown meaning is not the case here, as evidenced by the Examiner's proposed definitions of record, and by the Cody article, which uses a similar term ("angiotensin-mediated vasoconstriction"). It is respectfully submitted that the rejection is improper and should be withdrawn.

V. Rejection of Claims Under Obviousness-Type Double Patenting

Claims 1-10 were rejected as being allegedly obvious over claims 1-8, 1-15, and 1-3 of U.S. Pat. Nos. 5,721,263; 5,958,961; and 6,228,874, respectively, under the doctrine of obviousness-type double patenting. Office Action, p. 2. The present rejection is avoided by the terminal disclaimer and fee filed with this paper.

Conclusion

It is believed that the present reissue application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if she feels that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

Date Feb. 22, 2006 By _____

FOLEY & LARDNER LLP
Washington Harbour
3000 K Street, N.W., Suite 500
Washington, D.C. 20007-5143
Telephone: (202) 672-5569
Facsimile: (202) 672-5399

Stephen B. Maebius
Attorney for Applicants
Registration No. 35,264

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. § 1.136 and authorize payment of any such extensions fees to Deposit Account No. 19-0741.

Enclosure: SPE Y. Eyler, "*The Squeeze: Art and Enablement Together*," talk to the Biotech Customers on 10-29-2003; *In re Hogan*, 559 F.2d 595, 194 USPQ 527 (CCPA 1977); Cardiovascular Pharmacology, pp. 257-61, 415-16 (Michael J. Antonaccio, PhD, Ed., Raven Press New York 1984); and R.J. Cody, 47 Drugs 586-98 (April 1994).

IN THE MATTER OF THE APPLICATION OF JOHN PAUL HOGAN AND ROBERT L. BANKS

Patent Appeal No. 76-641.

UNITED STATES COURT OF CUSTOMS AND PATENT APPEALS

559 F.2d 595; 1977 CCPA LEXIS 125; 194 U.S.P.Q. (BNA) 527

July 28, 1977, Decided

PRIOR HISTORY: [**1]

Serial No. 181,185.

COUNSEL:

E. Eugene Innis, Bartlesville, Okl., Young & Quigg, Washington, D.C., attys, of record, for appellants.

Joseph F. Nakamura, Washington, D.C., for the Commissioner of Patents, Fred E. McKelvey, Washington, D.C., of counsel.

OPINIONBY:

MARKEY

OPINION: [*597]

MARKEY, Chief Judge.

This appeal is from the decision of the Patent and Trademark Office (PTO) Board of Appeals affirming various rejections, under *35 USC 102,* 103, 112 (first paragraph), and 132, of claims 13-15 in appellants' application No. 181,185 filed September 16, 1971 (the 1971 application) for "Solid Polymers of Olefins." *n1/* A main issue involves use of a "later state of the art" as evidence to support a rejection.

n1 / The real party in interest is Phillips Petroleum Company.

The 1971 application is said to be a continuation of application No. 648,364 filed June 23, 1967 (the 1967 application), in turn a "divisional" of application No. 558,530 filed January 11, 1956 (the 1956 application) *n2/.* The 1956 [**2] application is a continuation-in-part of application No. 476,306 filed December 20, 1954 and application No. 333,576 filed January 27, 1953 (the 1953 application).

n2 / The 1956 application is still pending. See note 3, infra.

We affirm in part, reverse in part, and remand with respect to certain rejections.

The Claims

Although the 1971 application discloses several polymers, the claims are limited: *n3/*

13. A normally solid homopolymer of 4-methyl-1-pentene. *n4/* [*598]

14. A polymer of claim 13 having a melting point in the range of 390 to 425 degree F.

15. A polymer of claim 13 which is wax-like and thermally stable as evidenced by substantially no decomposition at temperatures below about 700 degree F. as shown by Figure 5. *n5/*

n3 / At oral hearing, appellants' counsel stated that the 1956 application is involved in the "famous"polypropylene interference (see, e.g., *Standard Oil Co. v. Montedison, S.P.A.; 540 F.2d 611, 191 USPQ 657 (CA3 1976))* and "when that case got into the district court, we gave up on our hope for a generic product claim and filed applications to each one of the several species [of polymers]."

[**3]

n4 / 4-Methyl-1-pentene has a structural formula with carbon atoms numbered as follows:

1	2	3	4	5
CH2	=CH	-CH2	-CH	-CH3
			CH3	

n5 / "Figure 5" of the 1971 application is described infra.

The Disclosures

Appellants assert that, under the provisions of *35 USC 120, n6/* claims 13 and 15 are entitled to the benefit of the filing date of the 1953 application and claim 14 is entitled to the benefit of the filing date of the 1956 application.

n6 / § 120. Benefit of earlier filing date in the United States.

An application for patent for an invention disclosed in the manner provided by the first paragraph of section 112 of this title in an application previously filed in the United States by the same inventor *shall have the same effect, as to such invention, as though filed on the date of the prior application,* if filed before the patenting or abandonment of or termination of proceedings on the first application or on an application similarly entitled to the benefit of the filing date of the first application and if it contains or is amended to contain a specific reference to the earlier filed application. [Emphasis added.]

[**4]

The 1953 application discloses solid polymers made from 1-olefin monomers having a maximum chain length of eight carbon atoms and no branching nearer the double bond than the 4-position. Several olefin monomers which form such polymers are disclosed: ethylene, propylene, 1-butene, 1-pentene, 1-hexene, and 4-methyl-1-pentene.

A method of making such polymers using a catalyst containing chromium oxide on a silica-alumina support is described. The application includes twenty "examples" and twenty-five "tables" giving detailed information on: how to prepare, activate, use, and regenerate the catalyst; how to influence the molecular weight of the polymer products; what solvents or diluents to use in admixture with the olefin feed; what feed velocities, reaction pressures, reaction temperatures, and reaction times are operative; and certain physical and chemical characteristics of the polymer products.

Example I in the 1953 application includes this statement, which we designate as [A]:

[A]

4-Methyl-1-pentene gave tough, solid polymer which, however, was successfully expelled from the reactor in continuous-flow operation.

Example XVI refers to Figure 2 in the drawings, [**5] which is a graph showing thermal depolymerization curves for five polyolefin polymers and commercial polyisobutylene. Example XVI includes this statement, which we designate as [B]:

[B]

Whereas the former [commercial polyisobutylene] began to decompose at about 600 degree F, the latter (polymers of propylene, 1-butene, 1-pentene, 1-hexene, and 4-methyl-1-pentene) began to decompose at about 700-725 degree F.

Example XIX describes polymerizing 4-methyl-1-pentene "over chromia-alumina-silica catalyst" and states: "The 4-methyl-1-pentene polymer is a tough solid polymer suitable for a substitute for natural waxes."

The 1956 application is a continuation-in-part application and as filed contains most, but not all, of the information found in the 1953 application. Missing from the 1956 application as filed are statement [B] and the graph of Figure 2. Included in the 1956 application are the following new statements not present in the 1953 application, which we designate as [C] and [D]:

[C]

We have produced crystalline polymers of 4-methyl-1-pentene which have melting points in the range of 390 to 425 degree F.

[D]

1-Butene and 4-methyl-1-pentene can [**6] be polymerized in substantially the same manner as previously described and produce crystalline polymers. One sample of [*599] 4-methyl-1-pentene polymer thus obtained had a melting point of 394 degree to 421 degree F. A second similar polymer of 4-methyl-1-pentene produced in the same general manner had a melting point of 410 to 420 degree F.

The 1967 application, according to appellants' brief before the board, contains all of the disclosures relating to polymers of 4-methyl-1-pentene contained in the 1953 and 1956 applications. The 1971 application on appeal contains statements [A] and [B], the Figure 2 graph (now Figure 5), and statements [C] and [D].

The following table summarizes the disclosures:

Application (filing date)	Statement [A]	Statement [B]	Fig.2 (now Fig.5)	Statement [C]	Statement [D]
1-27-53	yes	yes	yes	no	no
1-11-56	yes	no	no	yes	yes
6-23-67	yes	yes	yes	yes	yes
9-16-71	yes	yes	yes	yes	yes

References

The references relied upon by the examiner and board were:

Haven	3,257,367	June 21, 1966 (filed June 23, 1955)
Edwards	3,299,022	January 17, 1967 (filed April 4, 1962)
Edwards	3,317,500	May 2, 1967 (filed October 2, 1963)

[**7]

Natta et al., *Rendiconti dell'Accademia Nazionale dei Lincei,* Series VIII, Vol. XIX, No. 6 (December 1955), pp.397-403.

Haven discloses a solid poly-4-methyl-1-pentene which is described as crystalline and, when oriented as a fiber, shows a melting point of 235 degree C. (455 degree F.).

Edwards ('022) describes a solid, amorphous, elastomeric homopolymer of 4-methyl-1-pentene. The patent states that a 1,4-type linkage *n7/* is almost exclusive, being over 95% of the repeating linkages in the homopolymer of 4-methyl-1-pentene, when polymerization using an aluminum chloride catalyst is conducted at temperatures below -60 degree C. The patent further states that "[it] has been thought possible heretofore to obtain polymerization of olefins only through [1,2-type linkage]" and that a "structural copolymer" is obtained which contains structural units of the 1,2-type linkage as well as of the 1,4-type linkage, when polymerization is conducted at a higher temperature.

n7 / A reference to the number 1 carbon of one molecule of 4-methyl-1-pentene (note 4, supra) linking to the number 4 carbon of another molecule of 4-methyl-1-pentene.

[**8]

Edwards ('500) discloses a 1,4-type polymer of 4-methyl-1-pentene in a cross-linked form having a molecular weight in excess of 1,000,000.

Natta et al. (Natta) discloses a poly-4-methyl-1-pentene which is crystalline and which has a melting point of 205 degree C. (401 degreef.) as determined by X-ray examination.

Rejections

The following rejections were affirmed by the board:

(1) Claims 13-15 under *35 USC 112,* first paragraph, *n8/* as "based on a non-enabling disclosure."

n8 / § 112. Specification.

The specification *shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art* to which it pertains, or with which it is most nearly connected, *to make and use the same* * * *. [Emphasis added.]

(2) Claim 14 under *35 USC 112,* first paragraph, as "based on a disclosure which does not teach how to prepare polymers having the claimed melting point [**9] range" of 390 to 425 degree F. [*600]

(3) Claim 14 under *35 USC 132* as "containing new matter in the combination of 'homopolymer' and the melting point range of 390 degree to 425 degree F."

(4) Claims 13-15 under *35 USC 102* as "fully met by Natta et al." (Natta).

(5) Claims 13 and 15 under *35 USC 102* as "fully met by Haven."

(6) Claim 14 under *35 USC 103* as "unpatentable over Haven."

The Examiner's Answer

(1) With respect to the rejection of claims 13-15 under *35 USC 112,* first paragraph, as based on a non-enabling disclosure, the examiner stated:

This rejection is premised on the fact that while the claims are generic in nature, applicants have, at best, only described a very limited species within the generic class. It is believed that the scope of the enablement provided by this specification is not commensurate with the scope of the protection sought. *In re Moore, [58 CCPA 1042, 439 F.2d 1232,] 169 USPQ 236* [(1971)].

* * * The disclosure * * * is non-enabling on how to prepare other species of this polymer such as those of Natta et al, Haven, Edwards (022) and Edwards (500) which, as far as this record is concerned, could not be prepared with [**10] the supported chromium oxide catalyst.

* * * The point is * * * that the claims are much broader than the polymers actually prepared in that about the only thing they have in common is that all are normally solid.

(2) With respect to the rejection of claim 14 under *35 USC 112,* first paragraph, as based on a disclosure which does not teach how to prepare polymers having the claimed melting point range of 390 to 425 degree F., the examiner stated that "[claim] 14 reads on a single 'species' of polymer which begins to melt at 390 degree F and is completely melted at 425 degree F or on any species that melt within this range." The examiner stated further that this rejection followed from a prior board decision (not of record) involving the 1967 application which held that the disclosure was non-enabling on how to make "a species" which had a melting point "of 410 to 420 degree F" (found in statement [D]). The examiner reasoned that the specification must also be non-enabling for "the only other 'species' which discloses a melting point, i.e., '394 to 421 degree F'" (found in statement [D]), and, therefore, "[if] the only disclosure of polymers having certain melting points [**11] is non-enabling, the raw disclosure of polymers having even broader melting points could not possibly be enabling," referring apparently to statement [C].

(3) With respect to the rejection of claim 14 under *35 USC 132* as containing new matter in the combination of "homopolymer" *n9/* with the melting point range of 390 degree to 425 degree F., the examiner explained that the only support for the temperature range appears in statement [C] and that the support for "homopolymers" presumably is derived from statement [D], but that the combination of these two limitations was created by amendment and, therefore, constituted new matter.

n9 / The Condensed Chemical Dictionary 448 (8th ed. 1971) defines "homopolymer" as "[a] polymer derived from a single monomer * * *."

(4) With respect to the rejection of claims 13-15 under *35 USC 102* as fully met by Natta, the examiner stated that appellants "agree" that the 4-methyl-1-pentene polymer of Natta "anticipates these claims" and that the "only issue" [**12] is whether Natta is "prior art to these claims."

Regarding claim 13, the examiner said that Natta is "a statutory bar" because nowhere in the 1971, 1967, or 1956 applications was there "an enabling disclosure" under *35 USC 112,* first paragraph, for the reasons cited above with respect to rejection (1). The examiner did not mention the 1953 application.

On claim 14, the examiner said that Natta "is prior art" for the reasons given for claim 13, for the additional reasons cited above with respect to rejections (2) and (3), [*601] and further because appellants' affidavit under *37 CFR 1.131* (Rule 131) "does not establish reduction to practice of this claim prior to December, 1955," which is Natta's publication date.

Regarding claim 15, the examiner said that Natta "is prior art" for the reasons given for claim 13 and that Natta is "a statutory bar" because the claimed subject matter is not disclosed in the 1956 application (i.e., statement [B] and the graph (now Figure 5) are not in that application).

(5) With respect to the rejection of claims 13 and 15 under *35 USC 102* as fully met by Haven, the examiner stated that "[the] Haven poly (4-methyl-1-pentene) would inherently [**13] possess the thermal stability properties of claim 15 in view of its high melting point" and that Haven is "a statutory bar to these claims" for the reasons given for Natta, above.

(6) With respect to the rejection of claim 14 under *35 USC 103* as unpatentable over Haven, the examiner stated that the oriented fiber of Haven having a melting point of 235 degree C. (455 degree F.) would be expected to have a higher melting point than the unoriented polymer of appellants and, therefore, the range of 390 to 425 degree F. recited in claim 14 would have been obvious. The examiner said Haven is "prior art" on this claim for the reasons given for Natta, above. The examiner also said that appellants' Rule 131 affidavit does not antedate Haven because the affidavit "does not establish reduction to practice or even conception of the generic range 390-425 degree F."

The Board

The board affirmed the rejections "for reasons essentially as given by the Examiner" which the board adopted as its own. The board then proceeded to add certain "comments for emphasis."

The board said that statement [C] "stands alone as a statement apparently unconnected with the preceding or following disclosure," [**14] and that "[it] gives no clue as to how a polymer of 4-methyl-1-pentene having the recited range of melting points is to be prepared * * *." The board concluded that "[the] disclosure is clearly non-enabling with respect to a teaching requisite to inform the artisan of how to make the claimed polymer."

The board further stated that the disclosure "is restricted to a teaching of how to make crystalline polymers," but that the claims are "not limited to a crystalline polymer of 4-methyl-1-pentene" but "encompasses an amorphous polymer as well, which is manifestly outside the scope of the enabling teaching present in the case."

The sole references to appellants' earlier applications, and to their Rule 131 affidavit, were contained in this paragraph:

Inasmuch as we sustain the Examiner's rejections under *35 U.S.C. 112* and 132, appellants are palpably not entitled to the benefit of the filing dates of their parent cases which have essentially the same relevant disclosure as present herein; the Natta et al. article and Haven patent are thus statutory bars and an affidavit under Rule 131 becomes inappropriate. Consequently, we affirm the rejections of the appealed claims under *35* [**15] *U.S.C. 102* as fully met by Natta et al. or Haven and do not reach nor decide the adequacy of the Rule 131 affidavit.

Appellants' Contentions

Appellants contend that the board committed "serious error" in affirming the rejection of claims 13-15 under *35 USC 112,* first paragraph, as based on a non-enabling disclosure. Appellants argue that the board failed to recognize the "pioneer" status *n10/* of appellants' invention and that the adequacy of their application should be judged by the state of the art as of its filing date. Relying upon *35 USC 120,* [*602] appellants assert the benefit of their January 27, 1953 filing date for claims 13 and 15 and their January 11, 1956 filing date for claim 14.

n10 / Their brief states: "The present specification describes a truly pioneer invention which is the *first* normally solid polymer of 4-methyl-1-pentene ever made." (Appellants' emphasis.) Whether appellants' invention is of "pioneer" status is not before us and bears no relation to our decision herein, though such status may influence the decision required on remand, as appears infra.

[**16]

Appellants argue that the board erred in affirming the rejection of claim 14 under *35 USC 112,* first paragraph, because their disclosure leaves "no doubt" as to how to make the polymers recited in claim 14. Appellants refer to statement [C], statement [D], and to examples which give specific conditions suitable for making polymers of 4-methyl-1-pentene, and argue that § 112 does not require a specification to contain a specific working example in order to be enabling.

With respect to the rejection of claim 14 under *35 USC 132* as containing new matter, appellants state that the board affirmed this rejection for the reasons given by the examiner, to wit, that the specification as originally filed does not support the combination of "homopolymer" with the recited melting point range because statement [C] includes copolymers and limiting that melting point range to homopolymers is "new matter." Appellants argue that the examiner and the board have considered statement [C] completely out of context with the rest of the specification.

Finally, appellants contend that claims 13 and 15 are entitled to the benefit of the filing date of the 1953 application which is prior to [**17] Natta and Haven, that claim 14 is entitled to the filing date of the 1956 application, which is less than one year subsequent to Natta and to the effective date of Haven, and that appellants' affidavit under Rule 131 shows prior completion of the invention of claim 14. Thus, appellants contend that claims 13 and 15 are free of the rejections under *35 USC 102* by virtue of the 1953 filing date and that claim 14 is free of rejections under *35 USC 102* and 103 because the Rule 131 affidavit removes Natta and Haven. Because the board declined to consider the adequacy of appellants' Rule 131 affidavit, appellants request that the case be remanded to the board for consideration of the affidavit if this court reverses the rejections under *35 USC 112* and 132.

The Solicitor

The solicitor supports the examiner and the board and further argues that appellants' claims cover a genus of homopolymers of 4-methyl-1-pentene, including both low and high molecular weight homopolymers; that "at best" appellants teach how to make only low molecular weight homopolymers; that it is possible in view of Natta, Haven, Edwards ('022), and Edwards ('500) to produce homopolymers having high molecular weights; [**18] and, therefore, "the enabling disclosure in the specification is not commensurate in scope with the breadth of the claims." The solicitor points out that appellants' Rule 131 affidavit shows that they possessed certain molecular weight data (showing a molecular weight of 1,800 for a polymer of 4-methyl-1-pentene) prior to the filing date of their 1956 application, yet such data

were not included in that application. Furthermore, the solicitor points to Edwards ('500) which discloses homopolymers of 4-methyl-1-pentene having molecular weights greater than 1,000,000. Thus, the solicitor contends that the examiner and the board made out a prima facie case that appellants' enabling disclosure is not commensurate in scope with the claims.

In response to appellants' argument that their disclosure should be judged by the state of the art as of its effective filing date, the solicitor states:

The references relied upon by the examiner to demonstrate the shortcomings of appellants' disclosure all have dates prior to the filing date of this [1971] application. Hence, until appellants establish that their present specification is sufficient, there is no need to determine what disclosure [**19] might have been sufficient in 1953 and 1954 when appellants' grandparent applications were filed. [Bracketed matter added.]

On the rejection of claim 14 as containing new matter, the solicitor argues that appellants do not disclose, in their 1971 application as filed, any homopolymers having [*603] melting points at the "outer limits" of the range 390 to 425 degreeF. and that "the only melting points disclosed are for homopolymers in the range of 394 to 421 degreeF. and 410 to 420 degreeF."

With respect to the prior art rejections, the solicitor states:

Consideration by the Court of the prior art rejections becomes necessary only if the lack of enablement rejection and new matter rejection are reversed. Since the Board had held that appellants' grandparent disclosures are essentially the same as the present disclosure with respect to claim 13 and 15, should the lack of enablement rejection and new matter rejection be reversed, the prior art rejections of claims 13 and 15 should also be reversed and the appeal should be remanded with respect to claim 14, because the Board did not rule on the sufficiency of the affidavit submitted by appellants under *37 CFR § 1.131* * [**20] * *.

OPINION

I. *Disregard of the Effect of 35 USC 120*

The board premised the rejection of claims 13-15 under *35 USC 112,* first paragraph, on insufficient enablement in appellants' 1971 application, disregarding entirely the statutory right of appellants under *35 USC 120.* That was clear error.

That the board looked only to appellants' 1971 application is clear from its statement quoted above. Because it sustained the rejections under *35 USC 112* and 132, the board said, "appellants are palpably not entitled to the benefit of the filing dates of their parent cases which have essentially the same relevant disclosure as present herein." The board did not specifically mention *35 USC 120* and its action deprived appellants of their rights under that portion of the statute.

In apparent recognition of the nature of the board's action, the solicitor argues, as above indicated, that "there is no need to determine what disclosure might have been sufficient in 1953" until after appellants have established "that their present specification is sufficient." The complete answer, of course, is that one who can establish sufficiency of a 1971 disclosure *has no need* to establish [**21] sufficiency of a 1953 disclosure, and no need to exercise his right to the benefit of *35 USC 120.*

Fully applicable to appellants' right under *35 USC 120* is this Supreme Court statement in *United States v. American Bell Telephone Co., 167 U.S. 224, 247 (1897):*

A party seeking a right under the patent statutes may avail himself of all their provisions, and the courts may not deny him the benefit of a single one. These are questions not of natural but of purely statutory right

The board's error in disregarding the effect of *35 USC 120* is highlighted by the legislative and judicial background of the statutory provision, which extends over more than a century. The Reviser's Note states: "This section represents *present law* not expressed in the statute * * *." (Emphasis added.) P.J. Federico's *Commentary on The New Patent Act, 35 USCA p.1, at p.31 (1954),* notes that the benefit provided by § 120 "was not specified in the old statute but was developed by decisions of the courts beginning with a decision of the *Supreme Court of 1864, Godfrey v. Eames, 68 U.S. 317.*" *Godfrey* v. *Eames* discusses the benefit accorded to the applicant in the following passage: [**22]

In our judgment, if a party choose to withdraw his application for a patent, and pay the forfeit, intending at the time of such withdrawal to file a new petition, and he accordingly do so, the two petitions are to be considered parts of *the*

same transaction, and both *as constituting one continuous application,* within the meaning of the law. [Emphasis added.] *[68 U.S. at 325-26.]* [*n11/*]

n11 / A requirement for copendency is now set forth in *35 USC 120.*

[*604]

The Supreme Court's explanation illuminates the meaning of "shall have the same effect" and clearly requires that we view appellants' applications as "parts of the same transaction" and "as constituting one continuous application" for the continuing subject matter recited therein.

We held in *In re Glass, 492 F.2d 1228, 1232, 181 USPQ 31, 34 (CCPA 1974),* that an applicant could not rely on what occurred in the art after his filing date because "application sufficiency under § 112, first paragraph, must be judged as of [**23] its filing date." *n12/* That principle applies equally to the PTO with respect to a continuing application entitled under § 120 to the benefit of an earlier filing date. No rational distinction can be made in the treatment accorded to the subject matter of an original application and to the same subject matter disclosed in a continuing application. Courts should not treat the same legal question, enablement under § 112, in one manner with respect to the applicant and in a different manner with respect to the examiner.

n12 / Accord, *In re Gunn, 537 F.2d 1123, 190 USPQ 402 (CCPA 1976); In re Scarbrough, 500 F.2d 560, 182 USPQ 298 (CCPA 1974).*

The examiner and the board, in support of the § 112 rejection, cited Natta, Haven, Edwards ('022), and Edwards ('500), not as *prior art,* but as *evidence* to prove appellants' disclosure non-enabling for "other species" of the claimed polymer, in an effort, as judicially required, to show why the scope of enablement was insufficient to support [**24] the claims. See, e.g., *In re Wertheim, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976); In re Armbruster, 512 F.2d 676, 185 USPQ 152 (CCPA 1975); In re Dinh-Nguyen, 492 F.2d 856, 181 USPQ 46 (CCPA 1974); In re Marzocchi, 58 CCPA 1069, 439 F.2d 220, 169 USPQ 367 (1971).* As thus implicitly recognized, the references would not have been available in support of a *35 USC 102* or 103 rejection entered in connection with the 1953 application. To permit use of the same references in support of the *35 USC 112* rejection herein, however, is to render the "benefit" of *35 USC 120* illusory. *n13/* The very purpose of reliance on § 120 is to reach back, to avoid the effect of intervening references. Nothing in § 120 limits its application to any specific grounds for rejection, or permits the examiner, denied use of references to reject or to require narrowing of a claim under § 102 or 103, to achieve the same result by use of the same references under § 112. Just as justice and reason require application of § 112 in the same manner to applicants and examiners, symmetry in the law, and evenness of its application, require that § 120 be held applicable to all bases for rejection, [**25] that its words "same effect" be given their full meaning and intent.

n13 / It would also exalt form over substance. If the present appellants had not filed continuing applications, the only filing date involved would be that of the 1953 application. To judge the 1971 application in isolation would have a chilling effect upon the right of applicants to file continuations. The 24 years of pendency herein may be decried, but a limit upon continuing applications is a matter of policy for the Congress, not for us. See *In re Henriksen, 55 CCPA 1384, 1395, 399 F.2d 253, 262, 158 USPQ 224, 231 (1968).* As presently constituted, the law as set forth in *35 USC 112* and 120 is the same for all applications, whether of long or short pendency.

The clear and unambiguous language of § 120 states that "[an] application * * * for an invention disclosed in the manner provided by the first paragraph of section 112 * * * in an application previously filed in the United States * * * *shall have the same effect, as* [**26] *to such invention, as though filed on the date of the prior application* * * *." (Emphasis added.) Thus, appellants' 1971 application should have been given "the same effect," i.e., it should have been tested for compliance with § 112, first paragraph, "as though filed on the date of the prior application," to wit, 1953 with respect to claims 13 and 15 *n14/* and 1956 with respect to claim 14.

n14 / Appellants allege entitlement to the 1953 filing date for claim 15. As discussed infra, claim 15 is not entitled to either the 1953 or 1956 filing date.

Because the board did not consider appellants' ancestral applications in affirming [*605] the rejections under § 112, first paragraph, in view of the cited references, those rejections must be reversed and the case remanded to permit consideration of enablement questions as of the proper filing date. *n15/*

n15 / It is immaterial under *35 USC 120* that the subject matter of claim 13 was not specifically claimed in the 1953 application. *In re Brower, 58 CCPA 724, 433 F.2d 813, 167 USPQ 684 (1970).*

[**27]

II. *Employment of a Later State of the Art in Testing For Compliance With 35 USC 112, First Paragraph*

The pendency since 1953 of appellants' applications, giving rise to concern over whether a claim may issue of breadth sufficient to encompass the later existing, "non-enabled" amorphous polymers of Edwards, and the PTO's application to the present facts of this court's statement in *In re Moore, 58 CCPA 1042, 439 F.2d 1232, 169 USPQ 236 (1971)* that "the scope of enablement" must be "commensurate with the scope of protection sought," impel clarification.

Citing *Moore,* the examiner stated that the § 112 rejection "is premised on the fact that while the claims are generic in nature, applicants have, at best, only described a very limited species within the generic class." Further, the examiner said "[the] disclosure * * * is non-enabling on how to prepare other species of this [claimed] polymer such as those of [the four cited references] which, as far as this record is concerned, could not be prepared with the supported chromium oxide catalyst." The board, in adopting the examiner's reasoning, recognized that its primary basis was the Edwards polymer: "The claims [**28] on appeal, however, are not limited to a crystalline polymer * * * but encompasses [sic] an amorphous polymer [of Edwards] as well which is manifestly outside the scope of the enabling teaching present in the case." Thus, amorphous polymers not having been, on this record, in existence in 1953, the examiner and the board focused on the later state of the art represented by the 1962 filing date of Edwards. *n16/*

n16 / According to the examiner and the board, Natta and Haven disclosed the same species disclosed by appellants and were applied under *35 USC 102* as statutory bars.

A later state of the art is that state coming into existence after the filing date of an application. This court has approved use of later publications as evidence of the state of art *existing on the filing date* of an application. *n17/* That approval does not extend, however, to the use of a later (1967, Edwards) publication disclosing a later (1962) existing state of the art in testing an earlier (1953) application [**29] for compliance with § 112, first paragraph. The difference may be described as that between the permissible application of later knowledge about art-related facts existing on the filing date and the impermissible application of later knowledge about later art-related facts (here, amorphous polymers) which did not exist on the filing date. Thus, if appellants' 1953 application provided sufficient enablement, considering all available evidence (whenever that evidence became available) of the 1953 state of the art, i.e., of the condition of knowledge about all art-related facts existing in 1953, then the fact of that enablement was established for all time and a later change in the state of the art cannot change it.

n17 / Where, for example, a later publication evidenced that, *as of an application's filing date,* undue experimentation would have been required, *In re Corneil, 52 CCPA 1718, 1724, 347 F.2d 563, 568, 145 USPQ 702, 705 (1965),* or that a parameter absent from the claims was or was not critical, *In re Rainer, 49 CCPA 1243, 1246 n.3, 305 F.2d 505, 507 n.3, 134 USPQ 343, 345 n.3 (1962),* or that a statement in the specification was inaccurate, *In re Marzocchi, 58 CCPA 1069, 1073 n.4, 439 F.2d 220, 223 n.4, 169 USPQ 367, 370 n.4 (1971),* or that the invention was inoperative or lacked utility, *In re Langer, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974),* or that a claim was indefinite, *In re Glass, supra, 492 F.2d at 1232 n.6, 181 USPQ at 34 n.6,* or that characteristics of prior art products were known, *In re Wilson, 50 CCPA 773, 311 F.2d 266, 135 USPQ 442*

(1962). Whatever may have been said enroute to decision in these cases, the fact situation in none of them established a precedent for permitting use of a later existing state of the art in determining enablement under *35 USC 112.*

[**30]

Rejections under § 112, first paragraph, on the ground that the scope of enablement is not commensurate with the scope of the [*606] claims, orbit about the more fundamental question: To what scope of protection is this applicant's particular contribution to the art entitled?

Though we do not reach the point on this appeal, we note appellants' argument that their invention is of "pioneer" status. The record reflects no citation of prior art disclosing a solid polymer of 4-methyl-1-pentene, which may suggest that appellants at least broke new ground in a broad sense. On remand, appellants may be found to have been in fact the first to conceive and reduce to practice "a solid polymer" as set forth in claim 13. As pioneers, if such they be, they would deserve broad claims to the broad concept. What were once referred to as "basic inventions" have led to "basic patents," which amounted to real incentives, not only to invention and its disclosure, but to its prompt, early disclosure. If later states of the art could be employed as a basis for rejection under *35 USC 112,* the opportunity for obtaining a basic patent upon early disclosure of pioneer inventions would be abolished. [**31]

The PTO has not challenged appellants' assertion that their 1953 application enabled those skilled in the art in 1953 to make and use "a solid polymer" as described in claim 13. Appellants disclosed, as the only then existing way to make such a polymer, a method of making the crystalline form. To now say that appellants should have disclosed in 1953 the amorphous form which on this record did not exist until 1962, would be to impose an impossible burden on inventors and thus on the patent system. There cannot, in an effective patent system, be such a burden placed on the right to broad claims. To restrict appellants to the crystalline form disclosed, under such circumstances, would be a poor way to stimulate invention, and particularly to encourage its early disclosure. To demand such restriction is merely to state a policy against broad protection for pioneer inventions, a policy both shortsighted and unsound from the standpoint of promoting progress in the useful arts, the constitutional purpose of the patent laws. See *In re Goffe, 542 F.2d 564, 191 USPQ 429 (CCPA 1976).*

In *In re Fisher, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970),* this court [**32] set forth the basic considerations respecting enablement and the potential for domination of future developments, describing the effect of predictability factors upon those considerations. We adhere to what was there said concerning the high level of predictability in mechanical or electrical environments and the lower level of predictability expected in chemical reactions and physiological activity. With respect to the erroneous use of a later state of the art in determining enablement, however, we make no distinction between fields of invention.

Consideration of a later existing state of the art in testing for compliance with § 112, first paragraph, would not only preclude the grant of broad claims, but would wreak havoc in other ways as well. The use of a subsequently-existing improvement to show lack of enablement in an earlier-filed application on the basic invention would preclude issuance of a patent to the inventor of the thing improved, and in the case of issued patents, would invalidate all claims (even some "picture claims") therein. Patents are and should be granted to later inventors upon unobvious improvements. Indeed, encouragement of improvements on prior inventions [**33] is a major contribution of the patent system and the vast majority of patents are issued on improvements. It is quite another thing, however, to utilize the patenting or publication of later existing improvements to "reach back" and preclude or invalidate a patent on the underlying invention.

If applications were to be tested for enablement under § 112 in the light of a later existing state of the art, the question would arise over how much later. An examiner could never safely call a halt and pass an application to issue. One who had slavishly copied the disclosed and claimed invention of a patent issued in 1965, for example, could resist an infringement action by insisting that a court hold the patent invalid because it was not enabling with respect to some third product which first came into [*607] existence, and thus came within the purview of the claim, in 1975.

The PTO position, that claim 13 is of sufficient breadth to cover the later state of the art (amorphous polymers) shown in the "references," reflects a concern that allowance of claim 13 might lead to enforcement efforts against the later developers. Any such conjecture, if it exists, is both irrelevant [**34] and unwarranted. The business of the PTO is patentability, not infringement. Like the judicially-developed doctrine of equivalents, designed to protect the patentee with respect to later-developed variations of the claimed invention, *n18/* the judicially-developed "reverse doctrine of equivalents," requiring interpretation of claims in light of the specification, *n19/* may be safely relied upon to preclude

improper enforcement against later developers. The courts have consistently considered subsequently existing states of the art as raising questions of infringement, but never of validity. It is, of course, a major and infinitely important function of the PTO to insure that those skilled in the art are enabled, as of the filing date, to practice the invention claimed.If, in the light of all proper evidence, the invention claimed be clearly enabled as of *that* date, the inquiry under § 112, first paragraph, is at an end.

n18 / See *Graver Tank & Mfg. Co. v. Linde Air Products Co., 339 U.S. 605, 85 USPQ 328 (1950).*

[**35]

n19 / See *Westinghouse v. Boyden Power Brake Co., 170 U.S. 537, 568-69 (1898).*

III. *The Rejections of Claim 13 Under 35 USC 102*

The filing date of appellants' 1953 application precedes Natta's publication date (December, 1955) by almost three years and it precedes Haven's effective date (June 23, 1955) as a prior art reference under *35 USC 102*(e) by more than two years.

Therefore, if claim 13 is entitled to the benefit of the 1953 filing date, Natta and Haven are not prior art references against claim 13 and the rejections under § 102 must fall. Because these rejections depend upon the same issue as that stated above for the § 112 rejection of claim 13, they are also reversed and the case is remanded to the PTO for consideration of the correct issue.

IV. *The Rejections of Claim 14*

A. *The First Rejection Under 35 USC 112, First Paragraph*

Claim 14 is not entitled to any date earlier than the 1956 filing date because, as appellants acknowledge, the disclosure to support [**36] claim 14 first appeared in the 1956 application. Each application since 1956 has contained the same basic disclosure with respect to claim 14.

What was said above, respecting the rejection of claim 13 under *35 USC 112,* first paragraph, is equally applicable to this rejection of claim 14, except for substitution of the *1956* filing date for the 1953 filing date, and, as indicated, this rejection of claim 14 is reversed and the case is remanded to the PTO for consideration of the correct issue.

B. *The Second Rejection Under 35 USC 112, First Paragraph*

The second rejection of claim 14 under *35 USC 112,* first paragraph, does not involve appellants' entitlement to an earlier filing date or the availability of any reference. It rests on the ground that the "disclosure does not teach how to prepare polymers having the claimed melting point range [390 degree to 425 degree F]."

Statement [C] teaches that appellants "have produced crystalline polymers of 4-methyl-1-pentene which have melting points in the range of 390 to 425 degree F." and statement [D] teaches that "4-methyl-1-pentene can be polymerized in substantially the same manner *as previously described* [to] [**37] produce crystalline polymers." (Emphasis added.) The "previously described" examples and teachnical information in the application give many details on how to make olefin [*608] polymers using a chromium oxide catalyst.

The examiner based this rejection on a prior board decision without explaining why the disclosure does not teach how to make the claimed invention. *n20/* The present board commented that statement [C] "stands alone," is "unconnected," and that it gives "no clue" on how to make the claimed polymer.

n20 / The examiner's answer did not base the rejection on the ground that claim 14 is limited to "a single 'species' of polymer which begins to melt at 390 degree F and is completely melted at 425 degree F." The examiner interpreted claim 14 as reciting this "species" *or* "any species that melt within its range."

The grounds advanced by the examiner and the board lack merit. Statement [C] does not "stand alone" and it is not "unconnected." Statement [C] must be read in light [**38] of the rest of the specification and it is clearly "connected," or related, to statement [D]. Statement [D] in turn is clearly connected to the detailed technical information on how to make olefin polymers. Neither the accuracy nor the sufficiency of *that* technical information has been questioned in this rejection. Thus, the examiner and the board effectively ignored statement [D] and the rest of the disclosure. This was error because the specification disclosure *as a whole* must be considered. *In re Moore, supra.*

The PTO not having carried its burden of establishing lack of enablement, this rejection of claim 14 under § 112, first paragraph, is reversed.

C.*The Rejection Under 35 USC 132*

Claim 14 was also rejected under *35 USC 132,* because "the combination of 'homopolymer' and the melting point range of 390 degree to 425 degree F." was considered "new matter" added by amendment to the 1971 application.

A new matter rejection under *35 USC 132,* predicated on claim language, is tantamount to a rejection for lack of a written description of the claimed invention under *35 USC 112,* first paragraph. *In re Bowen, 492 F.2d 859, 864, 181 USPQ 48, 52* [**39] *(CCPA 1974); In re Smythe, 480 F.2d 1376, 1385, 178 USPQ 279, 286 (CCPA 1973).* This court has held that claimed subject matter need not be described in haec verba in the application to satisfy the written-description-of-the-invention requirement. *In re Smith, 481 F.2d 910, 914, 178 USPQ 620, 624 (CCPA 1973).*

Statement [C] teaches that appellants "have produced crystalline polymers of 4-methyl-1-pentene which have melting points in the range of 390 to 425 degree F." One skilled in the art reading statement [C] would reasonably conclude that "polymers of 4-methyl-1-pentene" describes homopolymers (note 8, supra) of 4-methyl-1-pentene because that is the "necessary and only reasonable construction" to be given this statement. *Vogel v. Jones, 486 F.2d 1068, 1075, 179 USPQ 425, 431 (CCPA 1973); Binstead v. Littmann, 44 CCPA 839, 844, 242 F.2d 766, 770, 113 USPQ 279, 282 (1957).* If *copolymers* were being described, the sentence would refer to 4-methyl-1-pentene *and some other monomer.*

Accordingly, the rejection of claim 14 under *35 USC 132* is reversed.

D. *The Rejections Under 35 USC 102 and 103*

These prior art rejectios of claim 14 depend [**40] upon the availability as prior art of Natta and Haven. Because the PTO did not test for compliance with the first paragraph of § 112 as of the 1956 filing date, using the state of the art as of that date, the rejections of claim 14 under *35 USC 102* and 103 are reversed and we remand to the PTO so that the issue may be properly considered.

The filing date of appellants' 1956 application is *subsequent* to Natta's publication date (December, 1955) and to Haven's effective date (June 23, 1955). Therefore, if claim 14 is found on remand to be entitled to the benefit of the 1956 filing date, Natta and Haven would be available as prior art and the PTO should consider the adequacy of appellants' affidavit under *37 CFR 1.131* (Rule 131). [*609]

Appellants have never contended that Natta's polymer was not the same as theirs. To the contrary, throughout the prosecution history and before this court, appellants have maintained that Natta's polymer and their polymer are substantially identical. Therefore, if on remand claim 14 is found not to be entitled to the benefit of the 1956 filing date, Natta is a statutory bar to claim 14. *In re Foster, 52 CCPA 1808, 343 F.2d 980,* [**41] *145 USPQ 166 (1965), cert. denied, 383 U.S. 966, 149 USPQ 906 (1966).*

V. *The Rejections of Claim 15*

Claim 15 presents a situation different from that of claims 13 and 14 because, as appellants acknowledge, the disclosure to support claim 15 appears in the 1953 and the 1967 applications, but not in the 1956 application. Specifically, statement [B] and the Figure 2 graph showing the thermal depolymerization curves (Figure 5 in the 1971 application and referred to in claim 15) are not found in the 1956 application.

Thus, with respect to the subject matter of claim 15, there is a clear gap in the continuity of disclosure necessary to secure the benefit of § 120. As we stated in *In re Schneider, 481 F.2d 1350, 1356, 179 USPQ 46, 50 (CCPA 1973):*

[There] has to be a continuous chain of copending applications each of which satisfies the requirements of § 112 with respect to the subject matter presently claimed. See *In re deSeversky, 474 F.2d 671, 177 USPQ 144 (CCPA 1973).* There must be continuing disclosure through the chain of applications, without hiatus, to ultimately secure the benefit of the earliest filing date.

Accord, *In re Goodman, 476* [**42] *F.2d 1365, 177 USPQ 574 (CCPA 1973).*

Therefore, under § 120, claim 15 is entitled only to the benefit of the 1967 filing date, *n21/* and Natta is a statutory bar with respect to claim 15. *In re Foster, supra.* The rejection of claim 15 under *35 USC 102,* as anticipated by Natta, is therefore affirmed, and the rejections of claim 15 under *35 USC 112,* first paragraph, and under *35 USC 102* as fully met by Haven, are moot.

n21 / We refrain from comment on appellants' hypothetical argument that the 1956 application could be amended to add the material in the 1953 application.

Summary

(1) The rejections of claims 13 and 14 are *reversed.*

(2) The rejection of claim 15 under *35 USC 102* on Natta is *affirmed.* The remaining rejections of claim 15 are moot.

(3) The case is *remanded* for consideration of whether appellants' 1953 application was enabling with respect to claim 13 in view of the state of the art existing in 1953; whether appellants' 1956 application was enabling with respect [**43] to claim 14 in view of the state of the art existing in 1956, and, if so, whether appellants' affidavit under *37 CFR 1.131* was adequate to overcome Natta and Haven as references.

MODIFIED AND REMANDED

CONCURBY:

MILLER (In Part)

CONCUR:

MILLER, Judge, concurring in part.

I join the majority with respect to claim 15. However, I can only concur in the result reached by the majority with respect to claims 13 and 14.

The majority opinion properly holds that the board erred in considering the *later state of the art* in testing for compliance with the enablement requirement of *35 USC 112,* paragraph 1. However, in discussing this issue, it states:

The pendency since 1953 of appellants' applications, giving rise to concern over whether a claim may issue of breadth sufficient to encompass the later existing, "non-enabled" amorphous polymers of Edwards,... [impels] clarification.

It then "clarifies" the matter by stating:

The PTO has not challenged appellants' assertion that their 1953 application enabled those skilled in the art in 1953 to make and use "a solid polymer" as described in claim 13. Appellants disclosed, as the only then existing way to make [*610] such [**44] a polymer, a method of making the crystalline form... To restrict appellants to the crystalline form disclosed, under such circumstances, would be a poor way to stimulate invention.... To demand such restriction is merely to state a policy against broad protection for pioneer inventions....

Absent evidence to the contrary, the language in a patent application is to be interpreted as it would have been at the time the application was filed. Although the PTO may rely on later art, it must show that the language used in that art would have meant the same to one skilled in the art at the time the patent application was filed. As this court stated in *In re Voss,* F.2d , n.15, USPQ , n.15 (CCPA 1977):

[It] is clear from the quotation from *In re Fisher, 57 CCPA 1099, 1106, 427 F.2d 833, 838, 166 USPQ 18, 23 (1970),* set forth in [footnote 6 of *In re Glass, 492 F.2d 1228, 1232, 181 USPQ 31, 34 (CCPA 1974),]* that the PTO can rely on such later-issued patents and publications only if a showing is made that such claim language is the "language of the present art" as of the filing date of the application in question.

The majority [**45] opinion, in extended dicta, relies on *In re Goffe, 542 F.2d 564, 191 USPQ 429 (CCPA 1976),* for the proposition that restricting the claims to the crystalline form, preventing broad protection for a "pioneer" invention, would be "a policy both shortsighted and unsound from the standpoint of promoting progress in the useful arts...." However, the facts before us are clearly different from those in *Goffe.* There, the claim language, well defined in the prior art, clearly delineated the "outer boundaries" of the claimed subject matter, and the question was whether there was enablement for every embodiment within the scope of the claims. Here, the question is: *in light of the interpretation of the claim language at the time the patent application was filed,* what are the "outer boundaries" of the claims? Thus, *Goffe* is inapposite.

Contrary to the majority opinion, to permit the "outer boundaries" of a claim to be construed in light of later art, rather than in light of art at the time the patent application was filed, could well *impede* progress in the useful arts. For example, it would relegate a later species invention (*e.g.,* the solid amorphous homopolymer [**46] of Edwards) to a subservient position vis-a-vis an earlier species invention (*e.g.,* the solid crystalline homopolymer disclosed by appellants), even though the earlier inventor did not contemplate, much less enable, a generic invention, merely because the patent application for the earlier invention used a *broad* term which, at the time, had a meaning to one skilled in the art that was coextensive with the species.

The majority opinion notes that the PTO's arguments evidence a concern that allowance of claim 13 might lead to enforcement efforts against later developers, but states that any conjecture on this point is "both irrelevant and unwarranted," since "[the] business of the PTO is patentability, not infringement," and "the judicially-developed 'reverse doctrine of equivalents,' requiring interpretation of claims in light of the specification, may be safely relied upon to preclude *improper* enforcement against later developers." (Emphasis in original. Footnote omitted.) Two comments seem appropriate. First, in saying that "[to] restrict appellants to the crystalline form disclosed, under such circumstances, would be a poor way to stimulate invention," the majority [**47] opinion advocates a double standard: for the inventor, interpret the language of the claims against later developers in light of the later state of the art; but for the PTO, as held here, interpret such language against the inventor only in light of the state of the art at the time the application was filed. I do not agree that such a double standard is needed to spur invention. Second, the PTO, in managing its business of *patentability,* has a duty to construe the scope of the claims, to interpret the claim language in light of the specification and the art existing at the time the patent application was filed, and to determine whether the scope of enablement is commensurate with the scope of the claims. If, [*611] on remand, the PTO should determine that, at the time appellants' application was filed, one skilled in the art would have interpreted the phrase "solid homopolymer" broadly to include both crystalline and amorphous homopolymers, the PTO could, nevertheless, find that appellants' disclosure was only enabling to make a crystalline homopolymer and could properly reject claims 13 and 14 under the first paragraph of *35 USC 112* as of broader scope than the scope of [**48] enablement. On the other hand, if the PTO should determine that, at the time appellants' application was filed, one skilled in the art would have interpreted the phrase "solid homopolymer" to include only a crystalline homopolymer, a finding of enablement, at the time appellants' application was filed, to make a crystalline homopolymer would end the inquiry under § 112, first paragraph.

Cardiovascular Pharmacology

Second Edition

Editor

Michael J. Antonaccio, Ph.D.
Vice President
Cardiovascular Research
Bristol Myers Company
Evansville, Indiana

Raven Press ▪ New York

Raven Press, 1140 Avenue of the Americas, New York, New York 10036

Made in the United States of America

Library of Congress Cataloging in Publication Data
Main entry under title:

Cardiovascular pharmacology

Includes bibliographical references and index.
1. Cardiovascular agents. 2. Cardiovascular system--Diseases--Chemotherapy. I. Antonaccio, Michael J.
[DNLM: 1. Cardiovascular diseases--Drug therapy. 2. Cardiovascular system--Drug effects. 3. Cardiovascular agents--Therapeutic use. QV 150 C275]
RM345.C376 1984 615'.71 83-23087
ISBN 0-89004-872-X

The material contained in this volume was submitted as previously unpublished material, except in the instances in which credit has been given to the source from which some of the illustrative material was derived.

Great care has been taken to maintain the accuracy of the information contained in the volume. However, Raven Press cannot be held responsible for errors or for any consequences arising from the use of the information contained herein.

Cardiovascular Pharmacology, Second Edition,
edited by Michael Antonaccio.
Raven Press, New York © 1984.

Antihypertensive Drugs

Alexander Scriabine and David G. Taylor

Miles Institute for Preclinical Pharmacology, New Haven, Connecticut 06509

During the last two decades, significant advances have been made in the treatment of hypertension. These advances were made possible by new and highly effective antihypertensive drugs that were developed in the laboratories of pharmaceutical companies. The development of these drugs was not based on a better understanding of the pathogenesis of essential hypertension; our knowledge of the cause or causes of this disease remains remarkably poor. The antihypertensive drugs were found to modify physiological mechanisms of blood pressure control. In some instances, new drugs led to identification of previously unknown mechanisms of cardiovascular regulation, e.g., presynaptic control of norepinephrine release.

In accordance with their mechanisms of action, the available antihypertensive drugs can be classified as follows: (a) diuretics, (b) drugs that interfere with the renin-angiotensin system, (c) drugs that interfere with the sympathetic control of arterial pressure, and (d) smooth-muscle relaxants.

The size limitations for this chapter do not permit adequate coverage of all drugs with antihypertensive activity. For more detailed information on the pharmacology of antihypertensive drugs, readers are referred to a recent book on this subject (1). The major sites of antihypertensive actions of drugs are shown in Fig. 1, and the major mechanisms are listed in Table 1.

DIURETICS

Diuretics are commonly used in the initial therapy for hypertension. However, a higher diuretic efficacy does not imply higher antihypertensive efficacy. Loop diuretics (diuretics with the major site of action in the ascending limb of Henle's loop) are more effective than thiazides as diuretics, but not as antihypertensives. Thiazides are therefore preferred to loop diuretics in therapy for hypertension (2,3). The generic names, chemical structures, and clinical doses for some thiazide diuretics and related compounds are given in Table 2. The major pharmacological differences among these compounds involve their durations of action. Polythiazide, methyclothiazide, and chlorthalidone have the longest durations of action, which can exceed 24 hr.

Their longer durations of action are attributed to greater binding to plasma proteins and/or to greater lipophilicity and consequently greater tubular reabsorption (4). All known diuretics increase plasma renin activity, and consequently they increase the formation of angiotensin II and aldosterone; this tends to limit their antihypertensive effects. Therefore, combined use of diuretics with antihypertensives known to lower plasma renin activity (e.g., methyldopa, clonidine) is justified.

Most diuretics act by inhibiting tubular reabsorption of ions and water rather than by

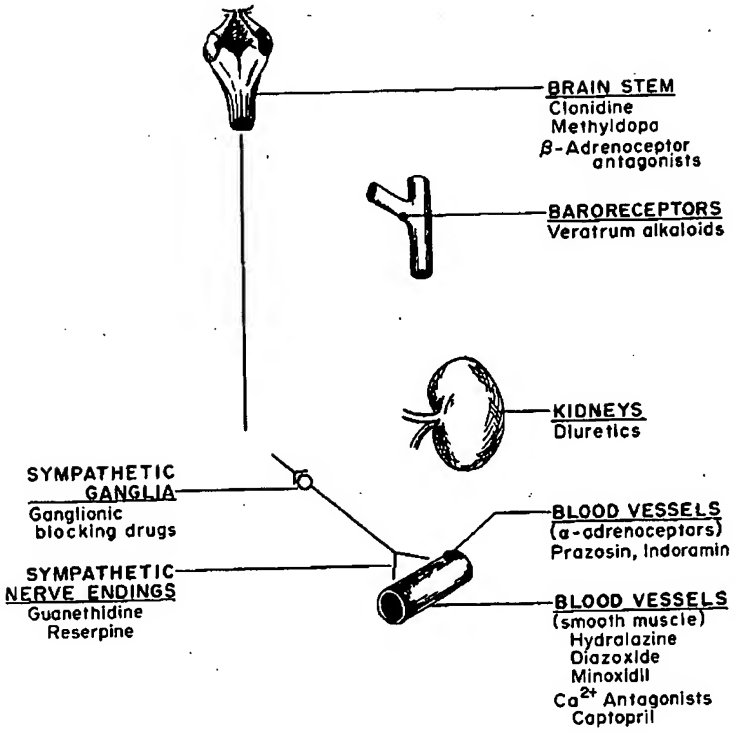


FIG. 1. Primary sites of action of antihypertensive drugs.

increasing glomerular filtration. There are at least four sites of action for diuretics in the renal tubules: proximal tubules, the ascending limb of Henle's loop, and lower and upper segments of distal tubules. The site of action of a diuretic is of clinical significance, because the saluretic effects of two diuretics are more likely to be additive if the drugs act at different tubular sites. Also, if a patient does not respond to one diuretic, he may respond to another diuretic acting at a different tubular site. The biochemical mechanisms involved in the inhibition of tubular transport of sodium and chloride by diuretics remain obscure, although some renal enzymes have been found to be inhibited by diuretics. The saluretic effect of acetazolamide is considered to be the consequence of inhibition of carbonic anhydrase. Thiazides also inhibit carbonic anhydrase, but their *in vitro* carbonic anhydrase inhibitory activity is not correlated with their *in vivo* saluretic effects (3). Furosemide, ethacrynic acid, and organomercurial diuretics inhibit Na^+-K^+-dependent ATPase *in vitro,* but no clear correlation between their ATPase inhibitory activity and saluretic activity has been established. Thiazides inhibit glycolysis *in vitro* (5), and chlorothiazide has been found to inhibit utilization of glucose in the dog aorta (6).

Various investigators have suggested that prostaglandins may mediate or modulate the renal effects of diuretics (7,8). Some diuretics inhibit 9-ketoreductase (9KR) or 15-hydroxyprostaglandin dehydrogenase and can therefore be expected to increase the availability of prostaglandins (9,10). Indomethacin or other inhibitors of cyclooxygenase reduce, but do not abolish, the effects of saluretics. The involvement of prostaglandins in the pharma-

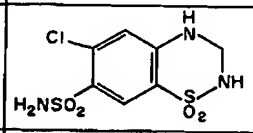
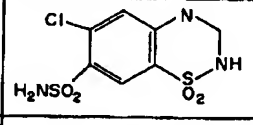
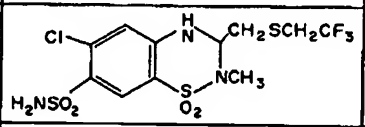
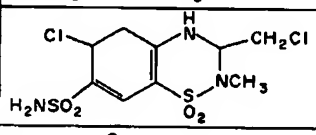
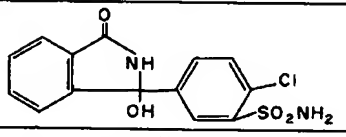
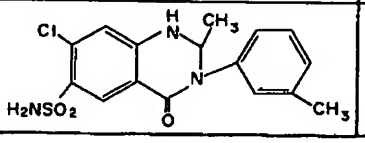
in vivo
hacrynic
; inhibit
but no
e inhibi-
as been
lysis *in*
n found
log aorta

ted that
late the
diuretics
ydroxy-
n there-
ailability
nacin or
luce, but
tics. The
pharma-

TABLE 1. *Proposed major mechanisms of action*

	Sympathetic control					Renin-angiotensin system inhibition	Vasodilator action	Buffer nerve enhancement
	Central α receptor activation	Ganglion blockade	Decrease NE release	α-Adrenoceptor blockade	β-Adrenoceptor blockade			
Captopril			X			X		
Veratrum alkaloids								X
Methyldopa	X		X					
Clonidine	X		X					X
Guanfacine	X		X					X
Guanabenz	X		X					
Trimethaphan camsylate		X						
Reserpine			X					
Guanethidine			X					
Prazosin				X				
Indoramin				X				
Propranolol	X				X	X		X
Labetalol				X	X			
Sodium nitroprusside							X	
Diazoxide							X	
Minoxidil							X	
Hydralazine							X	
Nifedipine							X	

TABLE 2. *Thiazides and thiazidelike diuretics commonly used in hypertension*

Generic Name	Structure	Daily Dose mg
Hydrochlorothiazide		25-200
Chlorothiazide		500-2000
Polythiazide		1-4
Methyclothiazide		2.5-10
Chlorthalidone		25-50 or 100 every second day
Metolazone		5-10

cological effects of diuretics may also be relevant to their antihypertensive activity. The acute antihypertensive effect of a new diuretic, 2-aminoethyl-4-(1,1-dimethylethyl)-6-10-iodophenol hydrochloride (MK-447) is reduced by indomethacin (11). The antihypertensive activity of diuretics was first shown in humans (12) and subsequently demonstrated in various animal models (13,14). An initial diuretic-induced decrease in plasma volume and subsequent reduction in vascular Na^+ content are the likely mechanisms of antihypertensive action. According to Friedman and Friedman (15), an increase in the sodium pool or in the "net Na^+ pumping activity" is likely to lead to hypertrophy of the vascular smooth-muscle cells and to vasoconstriction. Blaustein (16) suggested that an increase in ionized intracellular Na^+ may increase Ca^{2+} influx and decrease Ca^{2+} efflux out of vascular smooth-muscle cells, leading to vasoconstriction and to elevation of arterial pressure.

The major side effects of thiazide diuretics are hypokalemia, hyperuricemia, and a shift in the glucose tolerance curve toward a diabetic type. The loop diuretics furosemide, ethacrynic acid, and bumetanide produce the same side effects, but in addition they are more likely to produce severe electrolyte imbalance and dehydration than are thiazides. They can also produce a usually reversible loss of hearing. Serum lipid concentrations, primarily of β-lipoproteins, were reported to be elevated in patients receiving diuretics (17).

Diuretics alone cannot be expected to lower arterial pressure in more than 50% of hypertensive patients, but up to 80% of patients will respond to combined therapy with diuretics and drugs that interfere with the renin-angiotensin system or the sympathetic nervous system.

DRUGS AFFECTING THE RENIN-ANGIOTENSIN SYSTEM

Captopril

The involvement of the renin-angiotensin system in the pathogenesis of hypertension and control of arterial pressure has been suggested by various investigators over the last 80 years (18–20), but attempts to control hypertension by inhibitors of angiotensin II formation or by competitive antagonists of angiotensin II at vascular receptors have not been made until recently (21). Teprotide was the first inhibitor of the converting enzyme that was shown to lower arterial pressure in humans by intravenous (but not oral) administration (22). The first orally active inhibitor of the enzyme was captopril (Fig. 2). It was designed to bind to the active site of the converting enzyme in a manner similar to that of angiotensin I (20,23).

Because angiotensin-converting enzyme is identical with kininase II, the enzyme controlling the breakdown of bradykinin, captopril is capable of enhancing the vasodilator effect of bradykinin. Bradykinin enhancement could conceivably contribute to the mechanism of antihypertensive action of captopril (24,25), although, contrary to this view, Textor et al. (26) found that continuous infusion of angiotensin II blocked the antihypertensive effects of captopril, even when bradykinin responsiveness was enhanced 10-fold in rats. Furthermore, at therapeutic doses, captopril produces little elevation of plasma bradykinin in humans (27). Some investigators have suggested that bradykinin-induced increases in the formation and release of prostaglandins contribute partially to the captopril antihypertensive effects (28,29); however, this idea has not been supported by other studies in spontaneously hypertensive rats (30,31).

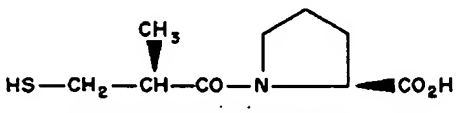


FIG. 2. Chemical structure of captopril.

In animals and humans, captopril inhibits the pressor effects of angiotensin I, but the pressor effects of angiotensin II are either unchanged or enhanced by captopril (20,32). In normotensive animals, the effect of captopril on the arterial pressure depends on the state of the salt balance. Greater effects are observed in sodium-depleted animals than in sodium-replete animals (20,33,34). In renin-dependent experimental renal hypertension (two-kidney renal-hypertensive rats) the onset of the antihypertensive action of captopril is immediate, but in one-kidney, one-clip renal hypertension a marked effect is not obtained until several days of therapy (20–23,30–35).

In spontaneously hypertensive rats, captopril has been shown to effectively lower arterial pressure (36). A recent report by Antonaccio and Kerwin (37) provides clues concerning the mechanism of action of captopril in this low-renin hypertensive model. In these studies, acute and chronic treatment with captopril quite selectively decreased the pressor responses, but not the cardiac responses, evoked by sympathetic outflow stimulation. The inhibitory effects of captopril were reversed by intravenous administration of angiotensin II plus indomethacin, but not nephrectomy. It was suggested that the reduced pressor responses and, quite possibly, the blood pressure levels produced by captopril were the results of decreased angiotensin-II-facilitated release of norepinephrine occurring at the prejunctional vascular sympathetic neuronal site.

In all species studied, the antihypertensive effect of captopril is associated with a reduction in total calculated peripheral vascular resistance, with either no effect or an increase in cardiac output. In hypertensive patients, peripheral resistance reductions are enhanced

Cardiovascular Pharmacology, Second Edition,
edited by Michael Antonaccio.
Raven Press, New York © 1984.

Calcium Antagonists

Ravinder K. Saini

The Squibb Institute for Medical Research, Princeton, New Jersey 08540

Medical treatment of patients with ischemic heart disease has improved greatly during the past two decades (1). Nitrates continue to play a vital role in therapy, although their mechanism(s) of action are still incompletely delineated after a century of use. The introduction of β blockers (specifically propranolol in this country) provided a second highly effective and extremely safe therapeutic modality for relieving angina, reducing blood pressure, and antagonizing certain cardiac arrhythmias (2,3). Recently, another new group of agents, used extensively in Europe and Japan for over 10 years, has shown promise in American clinical studies. These investigational drugs, which act by directly antagonizing the effect of calcium ions (Ca^{2+}) on both myocardial contractility and coronary arterial tone, are collectively known as Ca^{2+} antagonists. Their effect, according to Fleckenstein (4), is explained by selective blockade of the slow channel of the cell membrane—i.e., by interference with the transmembrane Ca^{2+} influx. However, recently some investigators (5,6) have suggested that other sites of action may be also important. The exact mechanism(s) of action of these agents are gradually being elucidated, and the new understanding is reflected in new terminology. Although many still use the term "Ca^{2+} antagonist," the more exact term "Ca^{2+} slow-channel blockers" was recently proposed.

Historically, the development of slow-channel blockers dates back to the early 1960s, at which time some German scientists (7,8) observed that prenylamine, a newly developed coronary dilator, and verapamil, another phenylalkylamine with coronary dilating properties, exerted negative inotropic effects on isolated cat and rabbit myocardium and also depressed cardiac performance in the canine heart-lung preparation. This potent cardiodepressant effect of these two new agents appeared to distinguish them from classic vasodilators, because drugs such as nitroglycerin and papaverine with potent smooth-muscle-relaxing properties depress cardiac muscle only at high concentrations. Because the inotropic and chronotropic effects of prenylamine and verapamil were quite opposite to those elicited by catecholamines, the new drugs were first believed to be adrenergic blocking agents (9,10). However, Fleckenstein et al. (11) were among the first to report that the effects of both prenylamine and verapamil differed from β-adrenergic receptor antagonists. They observed that both agents depressed cardiac contractility without altering the height of the contour of the monophasic action potential, and they concluded that the drugs acted as uncouplers of excitation-contraction coupling. The action of these drugs was attributed to inhibition of the influx of Ca^{2+} into the myocardial cells. Consequently, the agents were called Ca^{2+} antagonists (11).

ROLE OF CALCIUM IN THE HEART

Calcium ions are widely recognized as playing important roles in the overall maintenance

of homeostasis, in the contractile process of the heart, smooth muscle, and skeletal muscle, in glandular secretion, and in the release of neurotransmitters (4,12–14). In view of this, it is rather surprising that Ca^{2+} antagonists can be used therapeutically, having apparently a rather selective action on the cardiovascular system, without important side effects. It was a century ago that Sidney Ringer (15) established the importance of calcium in cardiac contraction. It is now well recognized that activation of contraction results from elevation of the intracellular concentration of calcium above 10^{-7} M. This, in turn, removes the inhibitory influence of the troponin-tropomyosin protein complex on the interaction between actin and myosin (16); actin filaments are displaced relative to myosin filaments, and contraction ensues (17) (Fig. 1). Thus, the calcium that enters the cell during the plateau of the action potential plays an essential role, coupling myocardial excitation to contraction, although there is some evidence that the transmembrane flux of calcium may merely trigger the release of larger quantities of the ion from intracellular stores and that it is the latter that actually activates the contractile mechanism (Fig. 1). Extracellular calcium is bound to the cell surface coat, and intracellular calcium is sequestered in the sarcoplasmic reticulum. In skeletal muscle, the calcium that triggers contraction comes mainly from internal stores in the plentiful sarcoplasmic reticulum. In cardiac muscle, the sarcoplasmic reticulum is not so plentiful, and the calcium current that flows from the cell surface to the interior during the action-potential plateau plays a more important role than in skeletal muscle. In vascular smooth muscle, membrane calcium may play an even more important role in contraction and maintenance of tone. The lumina of coronary and systemic arteries may be altered by changes in smooth-muscle tone induced by the movement of calcium across the membranes of smooth-muscle cells. If extracellular calcium is prevented from penetrating the cell membrane, muscular contraction will be prevented (18). In addition, vascular smooth muscle will relax, producing vasodilatation, and cardiac muscle will contract less powerfully. In addition to its role in contraction of heart muscle, calcium is important for the generation and conduction of the cardiac impulse. Reduction of calcium ions results in atrioventricular (A-V) block. In reentrant supraventricular tachyarrhythmias, the A-V node is considered to be the site of the recurrent pathway. Like digitalis, but by a different mechanism, agents that inhibit calcium flux tend to block conduction within the A-V node and depress reentrant circuits, thereby preventing or arresting supraventricular tachycardia. After-depolarizations are also inhibited by these agents. Thus, the genesis of extrasystoles is depressed. Overwhelming evidence has accumulated in the last two decades indicating that calcium ions are required during excitation in order to activate the biochemical processes that utilize adenosine triphosphate (ATP) for contraction. The rapid rise in free intracellular calcium resulting from the increased transmembrane calcium influx and a simultaneous liberation of calcium from endoplasmic stores initiates the splitting of ATP by the calcium-dependent ATPase of the myofibrils, so that phosphate-bond energy is transformed into mechanical work. Therefore, contractility is reversibly lost on calcium withdrawal. Thus, calcium ions not only trigger the contractile process but also control quantitatively the output of mechanical tension by regulating the amount of ATP that is metabolized during activity (20). The splitting of ATP will in turn give rise to intensified glycolytic and oxidative recovery processes that have to refill the high-energy phosphate stores. This explains that the whole chain of metabolic reactions following contraction is "calcium-sensitive."

ELECTROPHYSIOLOGY OF THE HEART

Although the precise mechanism of excitation-contraction coupling in most contractile tissues is still uncertain, information is availa-

Drugs

April 1994, Vol. 47, No. 4 (pp. 567-700)
ISSN: 0012-6667

FOCUS ON
Sumatriptan, Parnaparin, Levofloxacin

LEADING ARTICLE
Antihypertensive Drug Dosages

REVIEW ARTICLES
Gangliosides in Neurology
Renin Inhibitors and Angiotensin Antagonists

PRACTICAL THERAPEUTICS
Glycaemia Control in Diabetes
Psychotropic Drugs in HIV Infection

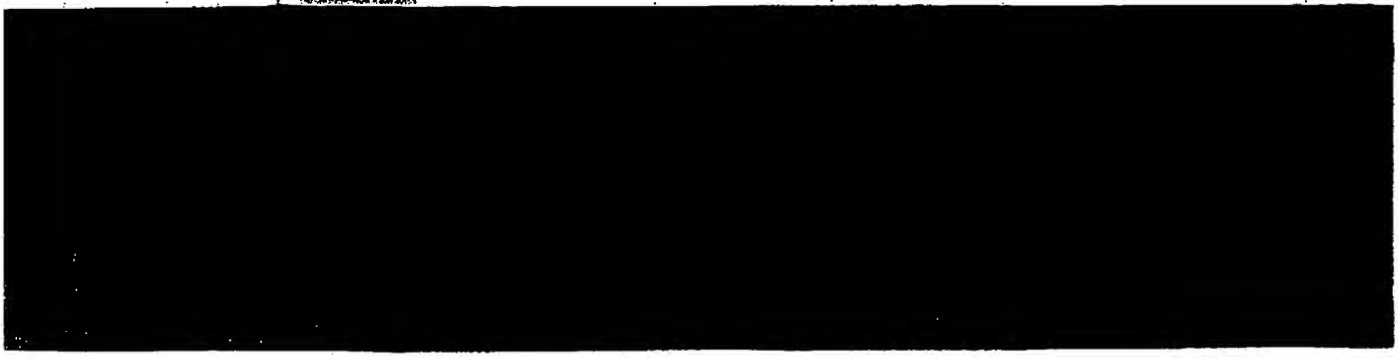
adis
INTERNATIONAL

CKLAND • CHESTER • HONG KONG • MILAN • OSAKA • PARIS • PHILADELPHIA • SYDNEY

Vol. 47, No. 4, 1994

Drugs

Drugs is indexed in 'Current Contents', 'Index Medicus' and 'Excerpta Medica'.



adis INTERNATIONAL

Drugs

Aim and Scope: The Journal aims to promote optimum drug therapy by providing a regular programme of review articles covering the most important aspects of clinical pharmacology and therapeutics. The focus of each issue of the Journal comprises two or more comprehensive Drug Evaluation reviews, which provide a detailed focus on the properties and place in therapy of both newer and established drugs. Other Review Articles and Leading Articles provide recommendations for specific clinical situations and overviews of contentious or emerging areas, respectively.

US Postmasters: Send address changes to: Adis International Inc., Suite F-10, 940 Town Center Drive, Langhorne, PA 19047, USA. Air freight and mailing in the US by Publications Expediting Inc., 200 Meacham Avenue, Elmont, NY 11003, USA.

Exclusive subscription agent in Japan: Technomics Inc., CPO Box 882, Tokyo 100-91, Japan.

Drugs (ISSN 0012-6667) is published monthly by Adis International Ltd, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 10, New Zealand. Annual subscription price: North & South America $US775; Europe SwF1260; Japan ¥131 750; rest of world $US775. (Further subscription information is given in the *General Information* page at the back of each issue.) Second class postage paid at Jamaica, NY 11431, USA. Printed in Hong Kong by Caritas Printing Training Centre.

Editorial Office and Editorial Inquiries: Adis International Limited, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 10, New Zealand.

REVIEW ARTICLE

Drugs 47 (4): 586-598, 1994
0012-6667/94/0004-0586/$06.50/0

The Clinical Potential of Renin Inhibitors and Angiotensin Antagonists

Robert J. Cody

Division of Cardiology, Department of Medicine, Ohio State University Medical Center, Columbus, Ohio, USA

Contents

Summary

The renin angiotensin system is a major contributor to the pathophysiology of cardiovascular diseases such as congestive heart failure and hypertension. For this reason, attempts to specifically block this system have been a pharmacological goal for over 25 years. Blockade of the renin system has been attempted at 3 pivotal sites: the rate limiting angiotensinogen-renin step, conversion of angiotensin I to angiotensin II, and the active receptor sites for the terminal products of angiotensin II and aldosterone.

Converting enzyme inhibitors have been successfully studied and utilised in clinical cardiovascular disorders, but questions persist regarding the specificity of their action. Thus, other more specific approaches remain under evaluation.

Inhibition of the action of renin on angiotensinogen was demonstrated with early inhibitory peptides and in experimental studies with specific antibodies. Most currently available renin inhibitors are nonpeptides, which nonetheless require intravenous administration. An oral renin inhibitor with clinical effects has been evaluated in early human trials. Like renin inhibitors and converting enzyme inhibitors, specific angiotensin antagonists were studied early in the course of renin system pharmacological blockade. Early angiotensin antagonists were limited, due to the requirement for intravenous administration and because of their short half-lives. They also had the potential for mixed agonist/antagonist physiological and pharmacological effects, which could result in a pressor, rather than a depressor, response.

The angiotensin receptor antagonists have the appeal of blocking the specific receptor at its target tissue site, analogous to other well described systems. Newer angiotensin antagonists do not have the limitations of the precursor peptides. Losartan (DUP753) is a specific angiotensin II AT_1 receptor antagonist. It is orally effective without agonist activity, and has high receptor

binding characteristics. Early studies indicate that it is a specific probe of the renin system, and is providing newer insights into the role of the renin system in cardiovascular disorders. Emerging clinical studies indicate that it is effective for blood pressure reduction and as a vasodilator.

Aldosterone antagonists such as spironolactone have been available for decades. Spironolactone is being used in an ongoing trial to assess the impact of combined converting enzyme and aldosterone inhibition. Newer aldosterone antagonists could add to targeted blockade of aldosterone without the adverse effects of the precursor compound, and the potential for combined specific renin system blockade.

It is difficult to divide an area of research endeavour into arbitrary stages of development. However, investigation of the role of the renin system in cardiovascular disease has ostensibly passed through 3 epochs (Cody 1992).

The first epoch was the identification of the renin system as an important endocrine system in pathophysiological disorders such as hypertension and congestive heart failure. The second epoch was the preliminary attempt to inhibit the renin system and identify both the physiological and pharmacological implications of inhibition. The initial endeavours in this regard included nonspecific agents, such as β-adrenergic blockade, and preliminary studies with angiotensin II antagonists, renin inhibitors, antirenin antibodies, and converting enzyme inhibitors (CEIs). The third epoch was the emergence and application of converting enzyme inhibitors. This class of agents has provided 15 years of valuable physiological information and clinical insight regarding not only the renin system, but also the fundamental abnormalities of cardiovascular disorders such as hypertension and heart failure.

With identification of newer mechanisms of action (Cody et al. 1993c; Dzau & Hersch 1990; Dzau & Pratt 1988), the further development of newer renin inhibitors and angiotensin antagonists, and the morbidity associated with increased renin system activity (Alderman et al. 1991), a fourth epoch of research has begun. This manuscript summarises the role of the renin system in cardiovascular homeostasis, and newer developments of renin system inhibition using approaches other than inhibition of angiotensin converting enzyme (ACE).

1. Renin-Angiotensin-Aldosterone (RAA) Pathway

The major components of the renin-angiotensin-aldosterone system are highlighted in figure 1.

Angiotensinogen is a 14-amino-acid α-2-globulin of hepatic origin, and is the substrate for the rate-limiting enzyme renin. Renin cleaves 4 amino acids from angiotensinogen, resulting in production of the decapeptide, angiotensin I. Two additional amino acids are subsequently cleaved from this decapeptide by ACE. ACE is a carboxypeptidase that was originally identified in the pulmonary circulation (Ng & Vane 1968), but subsequently has also been identified in blood vessel walls (Oparil et al. 1979). A carboxypeptidase of similar activity is responsible for degradation of the vasodilator bradykinin.

More recently, the key elements of the renin system have been identified in a variety of tissues, suggesting the importance of local tissue regulation of the pathway (Dzau 1987; Dzau & Hirsch 1990). Early in development, the converting enzyme was characterised as a carboxypeptidase of the kininase II group, an enzyme that cleaves 2 amino acids from angiotensin I, producing angiotensin II. The widespread characterisation of this enzyme in mammalian tissue has been summarised (Cushman et al. 1989).

In addition, this enzyme inhibited the degradation of bradykinin, with implications also for prostaglandin biosynthetic pathways (Zusman 1984). Despite the demonstration that a CEI would increase circulating bradykinin (Williams & Hollenberg 1977; Zusman 1984), CEIs became

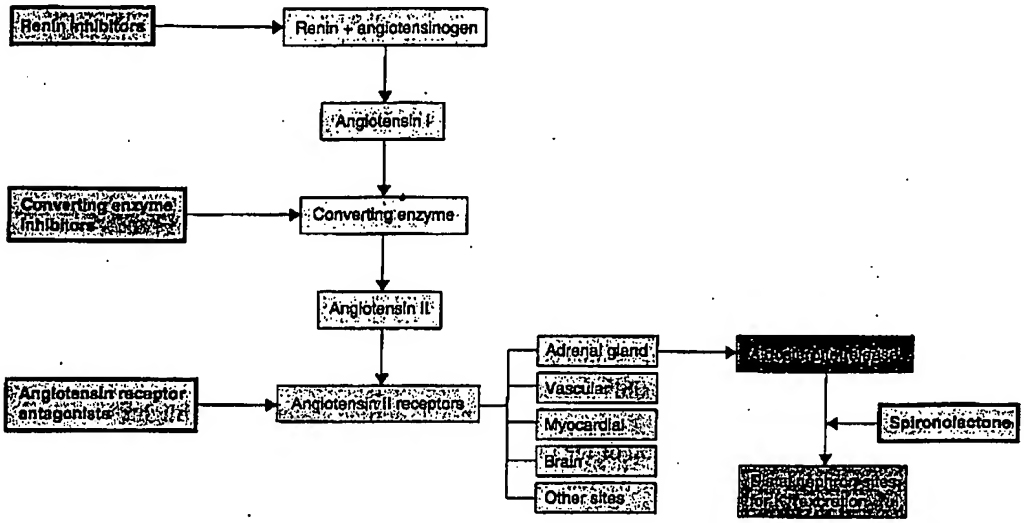


Fig. 1. Schematic summary of the major components of the renin-angiotensin-aldosterone cascade, highlighting the major classes of specific pharmacological agents developed to inhibit the renin system.

'ACE inhibitors,' emphasising the angiotensin mechanism.

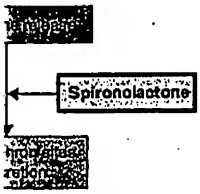
It is now virtually impossible to attend a clinical meeting without the question being raised: 'What about tissue ACE?' In fact, converting enzyme has always been a tissue enzyme. Initially identified in pulmonary tissue (Ng & Vane 1970), converting enzyme was later identified in vascular tissue (Naftilan et al. 1991; Oparil et al. 1979; Thurston & Swales 1974) and subsequently in many organ systems (Cushman et al. 1989; Dzau & Hirsch 1990). However, assay of tissue converting enzyme continues to demonstrate that its presence in the lung exceeds other tissue sites by orders of magnitude (Cushman et al. 1989).

In contrast, the importance of serum converting enzyme levels has not been established. Furthermore, converting enzyme, or carboxypeptidase, may have specific cellular effects (Hirsch et al. 1990). This enzyme, and the changes produced by its manipulation, may be of importance beyond the renin-specific effects of the enzyme. These issues may be relevant in view of recent clinical congestive heart failure trials. Unlike severe heart failure (Cody 1986, 1987, 1989; Cody et al. 1986), in early left ventricular dysfunction and early congestive heart failure the endocrine-renin system is often working within normal limits (Francis et al. 1990; Kubo et al. 1987).

The octapeptide, angiotensin II, generated by converting enzyme, is one of the most potent endogenous vasoconstrictors. In a situation where an inappropriate increase of vascular tone may accompany severe reduction of left ventricular function, the elaboration of angiotensin II would result in further impedance to forward flow, thereby further reducing cardiac output and regional flow. The manifestations of such reduced flow will depend on the vascular bed affected.

Potential benefits derived from blockade of angiotensin II in cardiovascular disorders are summarised in table I.

In addition to intense vasoconstriction, angiotensin II directly stimulates aldosterone release from the adrenal gland (Laragh & Sealey 1973), resulting in sodium and water retention. Sodium



ghting the major classes of

e severe heart failure
y et al. 1986), in early
and early congestive
enin system is often
(Francis et al. 1990;

sin II, generated by
the most potent en-
a situation where an
scular tone may ac-
left ventricular func-
ensin II would result
rd flow, thereby fur-
nd regional flow. The
ed flow will depend

from blockade of an-
ular disorders are

oconstriction, angio-
aldosterone release
gh & Sealey 1973),
r retention. Sodium

and volume expansion not only produce pulmonary and systemic venous congestion, but are also implicated in increased vascular stiffness. Aldosterone release also directly stimulates potassium excretion by the kidney.

2. The RAA System in Hypertension and Chronic Congestive Heart Failure

2.1 Vascular Tone

The dependence of vascular tone on angiotensin-mediated vasoconstriction can be identified in both animal models and clinical studies and the intensity of this effect can be modulated by the sodium status (Cody & Laragh 1988; Cody et al. 1986). In the state of sodium repletion, CEIs demonstrate minimal to moderate reduction of blood pressure.

However, in the state of sodium depletion, where the renin system is activated, a marked reduction of blood pressure occurs following converting enzyme inhibition. This effect has been demonstrated in healthy volunteers (Niarchos et al. 1979). In the sodium repleted state, minimal reduction of blood pressure is observed following converting enzyme inhibition. However, in the sodium depleted state, in which the renin system is activated, marked hypotension, to the induction of fainting and syncope, is evoked by converting enzyme inhibition.

In patients with congestive heart failure, this phenomenon has been identified using the additional stimulus of head-up tilt to evaluate the circulatory adaptation to postural gravitational stress (Cody et al. 1982a; Kubo & Cody 1983). In diuretic treated patients who received long term converting enzyme inhibition, a moderate reduction of blood pressure was seen. However, when these patients were tilted, a more marked hypotensive response was identified. In those patients with marked hypotension, this abnormal response was attenuated when tilt was repeated, following the rapid administration of saline into the central circulation. The dependence of vascular tone on angiotensin-mediated vasoconstriction is more clearly demonstrated during balanced sodium intake (Cody et al. 1986; Niarchos et al. 1979).

Table I. Clinical benefit derived from blockade of angiotensin II in cardiovascular disorders

Left ventricular structural and functional effects
● ↓ transmural wall stress
● ↓ compensatory dilatation and compensatory ↑ in end-diastolic and end-systolic volume
● improved coronary flow distribution in surface and transmural planes
Haemodynamic effects
● ↓ vascular resistance
● ↓ inotropic stimulation
● absence of chronotropic stimulation
Neurohormonal and paracrine effects
● ↓ circulating and tissue effects of angiotensin II
● diminished aldosterone and prevention of secondary sodium (and volume) retention
● ↓ circulatory catecholamines, improved baroreceptor function and restoration of sympathetic-parasympathetic balance
● diminished bradykinin degradation
Other effects
● blockade of cell growth effects of angiotensin II
● potential direct cellular effects of angiotensin converting enzyme (a carboxypeptidase)

Symbols: ↑ = increase; ↓ = decrease.

2.2 Sodium Excretion

The control of sodium excretion in humans is dependent on 2 variables of renal function: glomerular filtration rate and sodium reabsorption.

Glomerular filtration rate is abnormal in congestive heart failure. Sodium reabsorption is controlled by several factors including sympathetic nervous activity, aldosterone, and to a lesser degree, factors such as intrarenal distribution of blood flow, the balance of hydraulic and oncotic pressure, and atrial natriuretic peptide. The latter most likely is the elusive 'third factor' that has been postulated for many years.

As the vast majority of the filtered load of sodium is reabsorbed in the proximal tubule, the modulation of aldosterone activity at the distal tubule accounts for the maintenance of the balance

between dietary sodium intake and excretion on any given day (Laragh & Sealey 1973). However, in disorders such as congestive heart failure, little if any detectable sodium escapes into the urine, and this relationship is further obscured by the presence of diuretic therapy.

This relationship can be identified in patients in whom diuretics are withheld and sodium intake is balanced (Cody et al. 1986). Both plasma renin activity and urinary aldosterone excretion are increased during a low sodium intake. With an increase in daily sodium intake to 100 mEq, urinary sodium excretion increases and both plasma renin and urinary aldosterone excretion are suppressed. However, in those patients who continued to avidly retain sodium during oral loading, renin system activity remained increased. These data provide compelling evidence for the preservation of the macula densa signal for renin release in congestive heart failure. They also indicate that when the ingested sodium load is able to reach the macula densa, there is a reduction of the signal for renin release by the juxtaglomerular apparatus with subsequent reduction of aldosterone secretion, so that the ingested sodium load can be excreted.

3. Pharmacological Inhibition of the RAA System

3.1 Sites of Pharmacological Inhibition

If the renin system activation is physiologically relevant in cardiovascular disorders, then blockade of this system should result in favourable clinical and haemodynamic improvement.

The renin cascade can be interrupted at several levels (fig. 1). Release of renin by the juxtaglomerular apparatus can be inhibited by sympatholytic agents. This mechanism may partially explain the beneficial results observed when β-adrenergic blocking agents are administered to patients with hypertension or congestive heart failure.

The rate-limiting activities of renin may also be inhibited if an analogue of angiotensinogen is administered. Such peptides would compete with endogenous angiotensinogen for renin binding sites, thereby preventing the subsequent generation of angiotensin II (Burton et al. 1975). The effectiveness of competitive inhibitors was first studied *in vivo* using a primate model to account for species specificity (Burton et al. 1980; Cody et al. 1980a). Clinical trials of these renin inhibitory peptides have recently been initiated, and offer a new approach to RAA system inhibition.

The next step for potential inhibition of the renin cascade is at the level of converting enzyme. Identification of the beneficial effects of converting enzyme inhibition in heart failure were initially described with the nonpeptide, teprotide (Cody 1984). However, teprotide required intravenous administration and was not practical for long term therapy.

Subsequently, the oral ACE inhibitors captopril and enalapril were developed and extensively studied. Competitive antagonists which preferentially bind at the angiotensin II receptor are highly desirable and have also been a target for pharmacological development over many years (Turker et al. 1974).

Finally, spironolactone may be considered a competitive inhibitor of aldosterone at its binding sites in the distal nephron. In theory, this would provide a specific means to block the sodium-retaining properties of aldosterone.

3.2 Renin Inhibitory Peptides

Over the past 20 years, a series of agents have been developed that are capable of specifically blocking the RAA system. At present, there is no specific agent to block the release of renin from the juxtaglomerular cells. At best, nonspecific agents, principally β-adrenergic blockers, suppress the stimuli for renin release. On the other hand, β-adrenergic blocking agents have multiple sites of action, so that it would be difficult to delineate and attribute their primary focus to the inhibition of renin release from juxtaglomerular cells.

Since renin cleavage of angiotensinogen is the rate-limiting step of the RAA cascade, it would be desirable to specifically block this interaction (Haber 1989). In the past decade, 2 specific approaches

to the inhibition of this step in the cascade were developed. The first was peptides that structurally mimic endogenous angiotensinogen and therefore compete with it for binding to renin (Burton et al. 1975; Poulsen et al. 1976; Skeggs et al. 1968; Szelke et al. 1982). The second was the development of highly specific antibodies that would complex with renin, thereby limiting its ability to bind to angiotensinogen (Dzau et al. 1980).

The amino acid sequence of early renin inhibitory peptides was structurally and functionally similar to that of endogenous angiotensinogen (Burton et al. 1975; Poulsen et al. 1976; Skeggs et al. 1968), with high binding affinity (Burton et al. 1975; Cody et al. 1980a; Szelke et al. 1982; Zusman et al. 1983). Because these peptides were species-specific, their potential was initially limited to *in vitro* studies which documented renin inhibition. Subsequently, *in vivo* studies in primates were performed (Cody et al. 1980a; Szelke et al. 1982). These studies demonstrate reduction of blood pressure in the sodium depleted state and in renin dependent models of hypertension.

The use of monoclonal antibodies raised against human renin is an approach of potential benefit in physiological studies. However, therapeutic use would be limited by the cost and immunological concerns associated with parenteral monoclonal antibody administration. The early problem with development of antibodies that were active against human renin was the lack of purified human renin to serve as the antigen, and the production of sufficient antibody. An immunological approach, however, provides a novel perspective on the design of therapeutic agents.

In early human trials (Zusman et al. 1983), it was noted that a renin inhibitory peptide induced hypotension in healthy volunteers, particularly when they were sodium depleted or standing upright. The haemodynamic mechanism of blood pressure reduction was not clear, nor has it been determined whether this group of compounds has direct cardiodepressant or vagal activity.

The haemodynamic response to renin inhibitory peptides is primarily drawn from animal studies. In a model of renin dependent hypertension due to increased systemic vascular resistance (Cody et al. 1982b), bolus injection of a renin inhibitory peptide resulted in prompt reduction of blood pressure (Burton et al. 1980; Cody et al. 1980a). These results suggest that renin inhibitory peptides are likely to reduce blood pressure by reducing systemic vascular resistance.

More recently, the conceptual background and the design of specific renin inhibitory peptides, and data on their use, have been summarised (Haber et al. 1987; Hutchins & Greer 1991; Kleinert et al. 1991; Lunney et al. 1991; Raddatz et al. 1991; Rosenberg et al. 1991; Weber et al. 1991), and newer compounds have been described.

Enalkiren (A-64662) has been given intravenously, and has been shown to produce dose-related suppression of plasma renin activity. (Glassman et al. 1990). At doses of 0.3 and 1.2 mg/kg, dose-dependent reductions in blood pressure were demonstrated in diuretic treated hypertensive patients. These effects were prolonged despite a relatively short elimination phase (elimination half-life 1.6 hours). The antihypertensive effect of initial intravenous administration persisted for several days, and the mechanism for this persistent effect is not clear.

A limitation of renin inhibitory peptides is their poor oral bioavailability and rapid elimination (Fisher et al. 1991; Greenlee 1990; Kleinert 1989). The problems associated with the development of orally effective agents have been reported (Greenlee 1990), and the species specificity identified by experimental animal *in vivo* studies remains an issue (Humke et al. 1991). Nonetheless, progress has been made in development of these inhibitors (Greenlee 1987).

Immunological approaches to the inhibition of renin represent one of the early initial approaches to blocking the system. This approach has proved useful in the characterisation of the renin system (Michel et al. 1989). Yet, therapeutic approaches seem limited at the current time. Utilisation of modelling techniques support the design of renin inhibitors (Cooper et al. 1992; Hutchins & Greer

1991; Lunney et al. 1991; Patt et al. 1992; Rosenberg et al. 1991), and such an approach provides a conceptual and logical development of this class of therapy. Nonetheless, there is still a question as to whether the design and availability of specific renin inhibitory peptides will influence clinical approaches to therapy (Haber 1989). Such approaches to design are nonetheless yielding favourable preliminary results (Ashton et al. 1992; Atsuumi et al. 1992; Baker et al. 1992; Boyd et al. 1992; Martin et al. 1992; Ocain et al. 1992; Repine et al. 1992; Stein et al. 1992).

Design of specific inhibitors has also provided further identification of nonendocrine effects of renin in specific tissues (Norman et al. 1992; Okamura et al. 1992). As a result, newer, potent and selective orally active renin inhibitors are emerging (Doherty et al. 1992; Ii et al. 1991; Lacour et al. 1991; Shibasaki et al. 1991). YM-21065 produced a reduction of blood pressure and inhibited plasma renin activity in nonhuman primates in a dose-dependent manner (Shibasaki et al. 1991). This compound was effective after both intravenous and oral administration. Compared with captopril, short term oral administration of the renin inhibitor ES-8891 (Ii et al. 1991) produced a significant reduction of mean arterial pressure and plasma renin activity as well as plasma immunoreactive renin. This compound appeared to inhibit renin secretion from the kidney.

Data regarding the response to oral renin inhibitors in humans are emerging. Oral Ro 42-5892 was given to healthy volunteers in a dose-dependent fashion. In response to an intravenous infusion of this compound ranging from 0.001 to 1.0 mg/kg, plasma renin activity and angiotensin II were suppressed in a dose-dependent manner, while plasma active renin concentration increased. In healthy volunteers receiving oral Ro 42-5892, effects on the renin system were identified. Following 100, 600 or 1200mg of oral administration in a single-blind randomised fashion, plasma renin activity, angiotensin I and angiotensin II were significantly decreased within 30 minutes of oral administration. This effect was dose related (Camenzind et al. 1991).

These studies suggested, however, that sustained blockade of renin generation of angiotensin I resulted in an increase of actual renin secretion, as has been reported in other studies (Camenzind at al. 1991). As renin is the rate-limiting enzyme for the generation of angiotensin I and angiotensin II, this secondary stimulation of additional renin secretion could conceivably offset the favourable inhibitory effect.

In a separate set of experiments, Ro 42-5892 resulted in a reduction of plasma angiotensin II levels in healthy volunteers. When angiotensin II was administered together with a renin inhibitor, plasma angiotensin II levels increased until they were virtually identical to that produced by infusion of angiotensin II alone (Camenzind et al. 1991).

Ditekiren (U-71038) is another orally active renin inhibitor peptide (Epps et al. 1991; Greenfield et al. 1991). This compound, however, has had some unusual effects, including the potential for precipitation in aqueous solutions.

The intravenous and oral renin inhibitor GR70982 has also been evaluated in normotensive nonhuman primates, producing a dose-dependent inhibition of plasma renin activity. In renin dependent forms of primate hypertension, it also produced a dose-dependent reduction of mean arterial pressure with minimal effects on heart rate. When administered in an oral preparation, much larger doses are required to demonstrate inhibition of plasma renin activity (Gardner et al. 1991).

This identifies the potential problems that persist in the modelling and development of a renin inhibitory compound of either peptide or nonpeptide chemical structure. Nonetheless, the design of such compounds can be tested in pathophysiological conditions in humans (Neuberg et al. 1991). Thus, intravenous administration of enalkiren produces a vasodilator effect, ostensively by blocking the RAA system in patients with chronic congestive heart failure. This is associated with a favourable increase of cardiac output and function. Addi-

ıited (Camenzind et al.

l, however, that sus-
eration of angiotensin
ctual renin secretion,
r studies (Camenzind
rate-limiting enzyme
nsin I and angiotensin
n of additional renin
offset the favourable

riments, Ro 42-5892
ma angiotensin II lev-
ıen angiotensin II was
h a renin inhibitor,
s increased until they
ıat produced by infu-
ıe (Camenzind et al.

other orally active re-
t al. 1991; Greenfield
ıd, however, has had
lling the potential for
ations.
oral renin inhibitor
ıated in normotensive
ing a dose-dependent
activity. In renin de-
ertension, it also pro-
ction of mean arterial
s on heart rate. When
paration, much larger
onstrate inhibition of
.er et al. 1991).
ial problems that per-
velopment of a renin
er peptide or nonpep-
etheless, the design of
ed in pathophysiolog-
Neuberg et al. 1991).
ition of enalkiren pro-
tensively by blocking
with chronic conges-
ociated with a favour-
ıt and function. Addi-

tional studies are required to determine whether a similar effect can be produced with long term administration of renin inhibitors. However, from a theoretical standpoint, this would certainly seem quite feasible.

3.3 Angiotensin Receptor Antagonists

Angiotensin II analogues provide a means of renin system inhibition by directly competing with angiotensin II for tissue binding sites. Sarcosine substituted peptides (Hall et al. 1974) such as saralasin, the prototypical angiotensin II analogue, have been used for physiological studies.

There are 2 major reasons why the prototypical angiotensin antagonists were not practical as therapeutic agents in cardiovascular disorders. First, they had very short half-lives (Hall et al. 1974; Turker et al. 1974), and require continuous intravenous infusion. Secondly, their physiological activity depends on the basal level of endogenous angiotensin II at the receptor (Anderson et al. 1977; Cody 1984). That is, when the endogenous angiotensin II levels are low, these drugs act in an agonist fashion, mimicking the effects of exogenously administered angiotensin II and producing vasoconstriction. In situations of high endogenous angiotensin II activity, however, they displace the more potent endogenous angiotensin II from the receptor, and this antagonist activity results in a reversal of vasoconstriction (Cody et al. 1980b). The potential agonist effect, which increases vascular resistance, makes this group of drugs impractical for uniform treatment of cardiovascular disorders.

Angiotensin II antagonists have never achieved widespread therapeutic use in cardiovascular disorders. Systemic vascular resistance is reduced following intravenous administration of saralasin. This was especially true in patients in whom the renin system was markedly activated. These haemodynamic characteristics were observed in hypertension (Cody et al. 1980b), and congestive heart failure (Cody et al. 1984).

The unusual characteristics of saralasin provided additional insights. First, the response to saralasin could be modified by dietary sodium intake. Haemodynamic improvement occurred in patients placed on tight sodium restriction. When sodium intake was liberalised in the same patient, the response became agonistic, characterised by transient increases in systemic vascular resistance and pulmonary capillary wedge pressure, as well as decreases of cardiac index. Secondly, the haemodynamic response could be changed by the prior administration of converting enzyme inhibitors. In those patients demonstrating an initial antagonist response to saralasin, administration of either captopril or enalapril could subsequently transform the antagonist saralasin response to an agonist haemodynamic profile (Cody et al. 1984).

The ability to specifically block the effects of angiotensin II at its receptor sites is appealing. The paradigm for this approach is similar to that of the development of specific β- and α-adrenergic blockers to inhibit the effects of endogenous catecholamines. While inhibition of angiotensin II at its receptor does not preclude the possible subsequent stimulation of additional renin release, high binding affinity and specificity for an angiotensin II antagonist at a-downstream biochemical receptor site should obviate the physiological and pharmacological effects of such secondary stimulation.

As outlined above, the early development of angiotensin II antagonists was also limited by the requirement for intravenous administration in a manner similar to limitations with renin inhibitors. Recently, novel compounds have been produced which avoid the limitations of the intravenous precursors as they exist in nonpeptide forms (Bovy et al. 1989, 1990, 1991; Buhlmayer et al. 1991; Chang & Lotti 1990; Criscione et al. 1990; Timmermans et al. 1990; Wong et al. 1990c,d). These newer compounds are active after both intravenous and oral administration, with high binding affinity and specificity for the angiotensin II receptor. Unlike the prototypical intravenous angiotensin II antagonists, these compounds do not demonstrate agonist activity at the receptor.

Thus far, two of these compounds have been characterised rather extensively. The first com-

pound is losartan. Initially identified at Dupont Laboratories, this compound is now undergoing co-development by Dupont and Merck Sharp & Dohme Research Laboratories. Thus, losartan is also known as MK594. This compound has demonstrated specific binding to the AT_1 angiotensin II receptor, which has a predominant location in vascular and myocardial tissue. It produces dose-dependent reductions in blood pressure in experimental animal studies of hypertension (Timmermans et al. 1990). It is currently under investigation in clinical trials of both hypertension and congestive heart failure. The AT_1 receptor is located in brain, renal, myocardial, vascular, and adrenal zona glomerulosa tissue. The AT_2 receptor is identified in adrenal medullary sites (Herblin et al. 1991; Iwai & Inagami 1991). Blockade of the pressor response to angiotensin II is exemplified in figure 2.

A second angiotensin II antagonist has been well characterised. This is PD123319. This substance is specific for the AT_2 receptor population (Wong et al. 1990a). Because of receptor specificity, these 2 compounds have permitted better characterisation of the angiotensin receptors. These differences in receptor subtypes and antagonist interactions are readily defined (Wienen et al. 1992).

The absence of an agonist or pressor response to losartan is further supported by the fact that losartan actually blocks the pressor response to saralasin, the prototypical angiotensin II antagonist. This indicates that the agonist effect of saralasin is due to its angiotensin II-like characteristics at the AT_1 receptor (Wong et al. 1990b). Losartan has an immediate haemodynamic effect when given intravenously. There is a prolonged haemodynamic response to this compound, which is greater than its known half-life. This is likely due to the characteristics of its metabolite EXP3174 which also produces AT_1 receptor blockade and likely contributes to the duration of its haemodynamic effect (Wong et al. 1990b, c).

Preliminary studies with losartan indicate *in vivo* blockade of the angiotensin II AT_1 receptor,

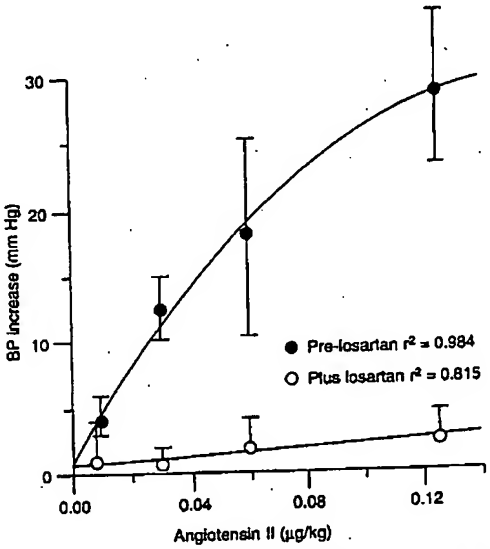
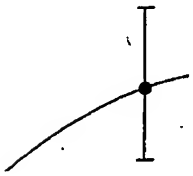


Fig. 2. The dose-dependent pressor response to intravenous administration of angiotensin II in normotensive adult rats. In the absence of losartan (DUP753), a dose-dependent increase in blood pressure occurs, with a peak increase of 28 ± 6mm Hg after administration of angiotensinogen II 0.125 µg/kg. Following intravenous administration of losartan 10 µg/kg, angiotensin II is again administered in the presence of losartan, and the anticipated pressor response to angiotensin II is virtually eliminated.

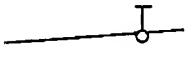
and effective physiological responses. In experimental models of hypertension, it produces both acute (Cody et al. 1991a,b) and chronic (Cody et al. 1993b) blood pressure reductions, mediated by reversal of vasoconstriction. The latter is associated with favourable effects on left ventricular performance (Cody et al. 1993a), and also attenuation of the development of left ventricular hypertrophy, when assessed prospectively (Hunnicutt et al. 1993).

Studies with these newer antagonists are ongoing and will likely produce a substantial renewal of interest in specific blockade of the angiotensin II receptor as a means to inhibit the renin system. These specific pharmacological probes of the renin system will also identify physiological effects of angiotensin II (Jaiswal et al. 1991), which would



Pre-losartan $r^2 = 0.984$

Plus losartan $r^2 = 0.815$



:08 0.12

/kg)

sponse to intravenous ad-
otensive adult rats. In the
se-dependent increase in
ease of 28 ± 6mm Hg after
.125 μg/kg. Following in-
0 μg/kg, angiotensin II is
sartan, and the anticipated
rtually eliminated.

esponses. In experi-
on, it produces both
nd chronic (Cody et
ıctions, mediated by
The latter is associ-
ı left ventricular per-
and also attenuation
tricular hypertrophy,
y (Hunnicutt et al.

ntagonists are ongo-
ıbstantial renewal of
of the angiotensin II
it the renin system.
al probes of the renin
siological effects of
1991), which would

otherwise be equivocal if deduced from the effects of ACE inhibitors. In addition, human studies with losartan have been initiated (Christen et al. 1991), and dose-ranging studies have been performed in sodium depleted healthy volunteers (Doig et al. 1993).

4. Aldosterone Antagonists

Aldosterone antagonists such as spironolactone have been available for decades. Although spironolactone was felt to be very specific, the clinical diuretic outcome was not impressive. Potassium excretion was substantially reversed. Adverse effects such as hyperkalaemia and gynaecomastia in males were adverse outcomes, particularly at the high dosages required for maximal clinical diuretic effect. Hyperkalaemia in patients with hypertension can be more intense when spironolactone is combined with a converting enzyme inhibitor. This is less frequently observed in patients with heart failure.

Use of spironolactone in the RALES (Randomized Aldactone Efficacy and Safety) trial will assess the impact of combined converting enzyme and aldosterone inhibition in patients with congestive heart failure. Newer aldosterone antagonists could add to targeted blockade of aldosterone without the adverse effects of the precursor compound, and the potential for combined specific renin system blockade.

5. Conclusion

The RAA system is pivotal in the development and progression of cardiovascular disease. Hence, pharmacological inhibition of this system has been attempted for many decades, and specific inhibitors of the renin system have been assessed *in vivo* for 20 years. These attempts have also provided specific pharmacological probes of the renin system that have aided the identification of the pathophysiology of disorders such as hypertension and congestive heart failure.

Although ACE inhibitors were the first class of specific renin system inhibitors to achieve oral therapeutic efficacy, newer classes such as renin inhibitors and angiotensin II antagonists, specifically losartan, are the most promising. The question which must now be addressed is whether these more specific antagonists, with appealing physiological and pharmacological activity, will offer sufficient clinical advantages to replace ACE inhibitors. Studies to assess this question are underway.

References

Alderman MH, Madhavan S, Ooi WL, Cohen H, Sealey JE, et al. Association of the renin-sodium profile with the risk of myocardial infarction in patients with hypertension. New England Journal of Medicine 324: 1098-1104, 1991

Anderson GH, Streeten DHP, Dalakos TG. Pressor response to 1-sar-8-ala-angiotensin II (saralasin) in hypertensive subjects. Circulation Research 40: 243-250, 1977

Ashton WT, Cantone CL, Meurer LC, Tolman RL, Greenlee WJ, et al. Renin inhibitors containing C-termini derived from mercaptoheterocycles. Journal of Medicinal Chemistry 35: 2103-2112, 1992

Atsuumi S, Nakano M, Koike Y, Tanaka S, Matsuyama K, et al. Renin inhibitors I: synthesis and structure-activity relationships of transition-state inhibitors containing homostatine analogues at the scissile bond. Chemical and Pharmaceutical Bulletin 40: 364-370, 1992

Baker WR, Fung AK, Kleinert HD, Stein HH, Plattner JJ, et al. Nonpeptide renin inhibitors employing a novel 3-aza(or oxa)-2,4-dialkyl glutaric acid moiety as a P2/P3 amide bond replacement. Journal of Medicinal Chemistry 35: 1722-1734, 1992

Bovy PR, Collins JT, Olins GM, McMahon EG, Hutton WC. Conformationally restricted polysubstituted biphenyl derivatives with angiotensin II receptors antagonist properties. Journal of Medicinal Chemistry 34: 2410-2414, 1991

Bovy PR, ONeal JM, Olins GM, Patton DR, McMahon EG, et al. Structure-activity relationships for the carboxy-terminus truncated analogues of angiotension II, a new class of angiotensin II antagonists. Journal of Medicinal Chemistry 33: 1477-1482, 1990

Bovy PR, Trapani AJ, McMahon EG, Palomo M. A carboxy-terminus truncated analogue of angiotensin II, [sar1]angiotensin II-(1-7)-amide, provides an entry to a new class of angiotensin II antagonists. Journal of Medicinal Chemistry 32: 520-522, 1989

Boyd SA, Fung AK, Baker WR, Mantei RA, Armiger YL, et al. C-terminal modifications of nonpeptide renin inhibitors: improved oral bioavailability via modification of physicochemical properties. Journal of Medicinal Chemistry 35: 1735-1746, 1992

Buhlmayer P, Criscione L, Fuhrer W, Furet P, de Gasparo M, et al. Nonpeptidic angiotensin II antagonists: synthesis and in vitro activity of a series of novel naphthalene and tetrahydronaphthalene derivatives. Journal of Medicinal Chemistry 34: 3105-3114, 1991

Burton J, Cody RJ, Herd JA, Haber E. Specific inhibition of renin by an angiotensinogen analog: studies in sodium depletion and renin-dependent hypertension. Proceedings of the National Academy of Sciences of the United States of America 77: 5476-5479, 1980

Burton J, Haber E, Poulsen K. The design of effective renin inhibitors. In Walter & Meienhofer (Eds) Peptides: chemistry, structure and biology, Ann Arbor Science Publishers Inc., Ann Arbor, 1975

Camenzind E, Nussberger J, Juillerat L, Munafo A, Fischli W, et al. Effect of the renin response during renin inhibition: oral Ro 42-5892 in normal humans. Journal of Cardiovascular Pharmacology 18: 299-307, 1991

Chang RS, Lotti VJ. Two distinct angiotensin II receptor binding sites in rat adrenal revealed by new selective nonpeptide ligands. Molecular Pharmacology 37: 347-351, 1990

Christen Y, Waeber B, Nussberger J, Porchet M, Borland RM, et al. Oral administration of DuP 753, a specific angiotensin II receptor antagonist, to normal male volunteers: inhibition of pressor response to exogenous angiotensin I and II. Circulation 83: 1333-1342, 1991

Cody RJ. Hemodynamic responses to specific renin angiotensin inhibitors in hypertension and heart failure: a review. Drugs 28: 144-169, 1984

Cody RJ. Conceptual and therapeutic approaches to inhibition of the renin-angiotensin system in chronic congestive heart failure. Journal of Cardiovascular Pharmacology 8 (Suppl. 1): S58-S65, 1986

Cody RJ. Assessment of neurohormonal parameters in congestive heart failure: determination of sodium and water regulation. In Morganroth & Moore (Eds) Congestive heart failure, pp. 25-37, Martinus Nijhoff, Boston, 1987

Cody RJ. Neurohormonal influences in the pathogenesis of congestive heart failure. In Weber K. (Ed.) Cardiology clinics heart failure, pp. 73-86, WB Saunders, Philadelphia, 1989

Cody RJ. Renin system inhibition: beginning the fourth epoch. Circulation 85: 362-364, 1992

Cody RJ, Brown DM, Hunnicutt M, Sinnathamby S. Effect of specific angiotensin II (AII) inhibition on LV function in the spontaneously hypertensive rat (SHR). American Journal of Hypertension 6: 27A, 1993a

Cody RJ, Brown DM, Hunnicutt M, Sinnathamby S. Hemodynamic and arterial compliance responses to chronic specific angiotensin II (AII) inhibition in the spontaneously hypertensive rat (SHR). American Journal of Hypertension 6: 3A, 1993b

Cody RJ, Burton J, Evin G, Poulsen K, Herd JA, et al. A substrate analog inhibitor of renin that is effective *in vivo*. Biochemical and Biophysical Research Communications 97: 230-235, 1980a

Cody RJ, Covit AB, Schaer GL, Laragh JH. Estimation of angiotensin II receptor activity in chronic congestive heart failure. American Heart Journal 108: 81-89, 1984

Cody RJ, Covit AB, Schaer GL, Laragh JH, Sealey JE, et al. Sodium and water balance in chronic congestive heart failure. Journal of Clinical Investigation 77: 1441-1452, 1986

Cody RJ, Fouad FM, Tarazi RC, Bravo EL. Hemodynamic effects of a new angiotensin antagonist (sarlthr8) angiotensin II in hypertensive man. Circulation 61: 338-344, 1980b

Cody RJ, Franklin KW, Kluger J, Laragh JH. Mechanisms governing the postural response, and baroreceptor abnormalities in chronic congestive heart failure: effects of acute and long term converting enzyme inhibition. Circulation 66: 135-141, 1982a

Cody RJ, Haas GJ, Binkley PF, Brown DM. Peripheral and aortic vascular responses to a specific angiotensin II antagonist, DUP 753, in the spontaneously hypertensive rat (SHR). American Journal of Hypertension 4: 32A, 1991a

Cody RJ, Haas GJ, Binkley PF, Brown DM. Hemodynamic and vascular characteristics of DUP753: A specific angiotensin II antagonist in the spontaneously hypertensive rat (SHR) (abstract). Journal of the American College of Cardiology 17: 202A, 1991b

Cody RJ, Laragh JH. The renin-angiotensin-aldosterone system in chronic congestive heart failure: pathophysiology and implications for treatment. In Cohn (Ed.) Drug treatment of heart failure, pp. 79-104, Advanced Therapeutics Communications International, Secaucus, 1988

Cody RJ, Livingston W, Brown DM, Hunnicutt M, Sinnathamby S. Angiotensin AT1 blockade suppresses myocardial, but not aortic endothelin-1 transcription in pressure overload ventricular failure. Circulation 88 (Suppl. I): I-294, 1993c

Cody RJ, Rodger RF, Hartley LH, Burton J, Herd JA. Acute hypertension in a non-human primate: humoral and hemodynamic mechanisms. Hypertension 4: 219-225, 1982b

Cooper J, Quail W, Frazao C, Foundling SI, Blundell TL, et al. X-ray crystallographic analysis of inhibition of endothiapepsin by cyclohexyl renin inhibitors. Biochemistry 31: 8142-8150. 1992

Criscione L, Thomann H, Whitebread S, de Gasparo M, Buhlmayer P, et al. Binding characteristics and vascular effects of various angiotensin II antagonists. Journal of Cardiovascular Pharmacology 16 (Suppl. 4): S56-S59, 1990

Cushman DW, Wang FL, Fung WC, Harvey CM, DeForrest JM. Differentiation of angiotensin-converting enzyme (ACE) inhibitors by their selective inhibition of ACE in physiologically important target organs. American Journal of Hypertension 2: 294-306, 1989

Doherty AM, Sircar I, Kornberg BE, Quin III J, Winters RT, et al. Design and synthesis of potent, selective, and orally active fluorine-containing renin inhibitors. Journal of Medicinal Chemistry 35: 2-14, 1992

Doig JK, MacFadyen RJ, Sweet CS, Lees KR, Reid JL. Dose-ranging study of the angiotensin type I receptor antagonist losartan (DUP753/MK954) in salt-deplete normal man. Journal of Cardiovascular Pharmacology 21: 732-738, 1993

Dzau VJ. Implications of local angiotensin production in cardiovascular physiology and pharmacology. American Journal of Cardiology 59: 59A-65A, 1987

Dzau VJ, Hirsch AT. Emerging role of the tissue renin-angiotensin systems in congestive heart failure. European Heart Journal 11 (Suppl. B): 65-71, 1990

Dzau VJ, Kopelman RI, Barger CA, Haber E. Renin-specific antibody for study of cardiovascular homeostasis. Science 207: 1091-1093, 1980

Dzau VJ, Pratt RE. Renin gene expression, biosynthesis, and cellular pathways of secretion. Clinical Physiology and Biochemistry 6: 210-216, 1988

Epps DE, Poorman RA, Mandel F, Schostarez HJ. Determination of dissociation constants of high affinity (pM) human renin inhibitors: application to analogues of ditekiren (U-71,038). Journal of Medicinal Chemistry 34: 2107-2112, 1991

Fisher JF, Harrison AW, Bundy GL, Wilkinson KF, Rush BD, et al. Peptide to glycopeptide: glycosylated oligopeptide renin inhibitors with attenuated in vivo clearance properties. Journal of Medicinal Chemistry 34: 3140-3143, 1991

Francis GS, Benedict C, Johnstone DE, Kirlin PC, Nicklas J, et al. for the SOLVD Investigators. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure: a substudy of the studies of left ventricular dysfunction (SOLVD). Circulation 82: 1724-1729, 1990

Gardner CJ, Twissel DJ, Charlton PA, Cherry PC. Acute and chronic effects of renin inhibitor GR 70982 in the conscious marmoset. European Journal of Pharmacology 192: 329-335, 1991

Glassman HN, Kleinert HD, Boger RS, Moyse DM, Griffiths AN, et al. Clinical pharmacology of enalkiren, a novel, dipeptide renin inhibitor. Journal of Cardiovascular Pharmacology 16 (Suppl. 4): S76-S81, 1990

Greenfield JC, Loux SJ, Sood VK, Jenkins KM, Davio SR. In-vitro evaluation of the plasma and blood compatibility of a parenteral formulation for ditekiren, a novel renin inhibitor pseudopeptide. Pharmacological Research 8: 475-479, 1991

Greenlee WJ. Renin inhibitors. Pharmacological Research 4: 364-374, 1987

Greenlee WJ. Renin inhibitors. Medical Research Reviews 10: 173-236, 1990

Haber E. Why renin inhibitors? American Journal of Hypertension 7: S81-S86, 1989

Haber E, Hui KY, Carlson WD, Bernatowicz MS. Renin inhibitors: a search for principles of design. Journal of Cardiovascular Pharmacology 10 (Suppl. 7): S54-S58, 1987

Hall MM, Khosla MC, Khairallah PA, Bumpus FM. Angiotensin analogs: the influence of sarcosine substituted in position 1. Jour-

nal of Pharmacology and Experimental Therapeutics 188: 222-228, 1974
Herblin WF, Chiu AT, McCall DE, et al. Angiotensin II receptor heterogeneity. American Journal of Hypertension 4: 299S-302S, 1991
Hirsch AT, Pinto YM, Schunkert H, Dzau VJ. Potential role of the tissue renin-angiotensin system in the pathophysiology of congestive heart failure. American Journal of Cardiology 66: 22D-32D, 1990
Humke U, Levens N, Wood J, Hofbauer K. Responses to renin inhibition in conscious primates. American Journal of Physiology 261: F179-F186, 1991
Hunnicutt M, Alton ME, Haas GJ, Brown DM, Cody RJ. Attenuated development of left ventricular hypertrophy (LVH) with long term DUP753 in the spontaneously hypertensive rat (SHR). American Journal of Hypertension 6: in press, 1993
Hutchins C, Greer J. Comparative modelling of proteins in the design of novel renin inhibitors. Critical Reviews in Biochemistry and Molecular Biology 26: 77-127, 1991
Ii Y, Murakami E, Hiwada K. Effect of renin inhibitor, ES-8891, on renal renin secretion and storage in the marmoset: comparison with captopril. Journal of Hypertension 9: 1119-1125, 1991
Iwai N, Inagami T. Regulation of the expression of the rat angiotensin II receptor mRNA. Biochemical and Biophysical Research Communications 182: 1094-1099, 1991
Jaiswal N, Diz DI, Tallant EA, Khosla MC, Ferrario CM. The nonpeptide angiotensin II antagonist DuP 753 is a potent stimulus for prostacyclin synthesis. American Journal of Hypertension 4: 228-233, 1991
Kleinert HD. Renin inhibitors: discovery and development. An overview and perspective. American Journal of Hypertension 2: 800-808, 1989
Kleinert HD, Baker WR, Stein HH. Renin inhibitors. Advanced Pharmacology 22: 207-250, 1991
Kubo SH, Clark M, Laragh JH, Borer JS, Cody RJ. Identification of normal neurohormonal activity in mild congestive heart failure and the stimulating effect of upright posture and diuretics. American Journal of Cardiology 60: 1322-1328, 1987
Kubo SH, Cody RJ. Circulatory autoregulation in chronic congestive heart failure. Response to tilt in 41 patients. American Journal of Cardiology 52: 512-518, 1983
Lacour C, Roccon A, Cazaubon C, Richaud JP, Segondy D, et al. A pharmacodynamic study of the renin inhibitor SR 43,845, administered intratracheally in conscious cynomolgus monkeys. Journal of Hypertension.(Suppl. 9): S384-S385, 1991
Laragh JH, Sealey JE. The renin-angiotensin aldosterone hormonal system and regulation of sodium, potassium, and blood pressure homeostasis. In Orloff & Berliner (Eds) Handbook of renal physiology, section 8, pp. 831-908, American Physiological Society, Washington, 1973
Lunney EA, Humblet CC, Repine JT, Blundell TL, Cooper JB, et al. Molecular modelling of renin inhibitor P2 substituents. Advances in Experimental Medicine and Biology 306: 391-394, 1991
Martin SF, Austin RE, Oalmann CJ, Baker WR, Condon SL, et al. 1,2,3-trisubstituted cyclopropanes as conformationally restricted peptide isosteres: application to the design and synthesis of novel renin inhibitors. Journal of Medicinal Chemistry 35: 1710-1721, 1992
Michel JB, Guettier C, Reade R, Sayah S, Corvol P, et al. Immunologic approaches to blockade of the renin-angiotensin system: a review. American Heart Journal 117: 756-767, 1989
Naftilan AJ, Zuo WM, Inglefinger J, Ryan Jr TJ, Pratt RE, et al. Localization and differential regulation of angiotensinogen mRNA expression in the vessel wall. Journal of Clinical Investigation 87: 1300-1311, 1991
Neuberg GW, Kukin ML, Penn J, Medina N, Yushak M, et al. Hemodynamic effects of renin inhibition by enalkiren in chronic congestive heart failure. American Journal of Cardiology 67: 63-66, 1991
Niarchos AP, Pickering TG, Case DB, Sullivan P, Laragh JH. Role of the renin-angiotensin system in blood pressure regulation: the cardiovascular effects of converting enzyme inhibition in normotensive subjects. Circulation Research 45: 829-837, 1979
Ng KKF, Vane JR. Fate of angiotensin I in the circulation. Nature 218: 144-150, 1968
Ng KKF, Vane JR. Some properties of angiotensin converting enzyme in the lung in vivo. Nature 225: 1142-1144, 1970
Norman JA, Hadjilambris O, Baska R, Sharp DY, Kumar R. Stable expression, secretion, and characterization of active human renin in mammalian cells. Molecular Pharmacology 41: 53-59, 1992
Ocain TD, Deininger DD, Ruso R, et al. New modified heterocyclic phenylalanine derivatives: incorporation into potent inhibitors of human renin. Journal of Medicinal Chemistry 35: 823-832, 1992
Okamura T, Aimi Y, Kimura H, Murakami K, Toda N. Existence of renin in the endothelium of human artery. Journal of Hypertension 10: 49-53, 1992
Oparil S, Koerner T, O'Donaghue JK. Mechanism of angiotensin I converting enzyme inhibition by SQ20881 (Glu-Trp-Pro-Arg-Pro-Gln-Ile-Pro-Pro) in vivo: further evidence for extrapulmonary conversion. Hypertension 1: 13-22, 1979
Patt WC, Hamilton HW, Taylor MD, Ryan MJ, Taylor Jr DG, et al. Structure-activity relationships of a series of 2-amino-4-thiazole-containing renin inhibitors. Journal of Medicinal Chemistry 35: 2562-2572, 1992
Poulsen K, Burton J, Haber E. Competitive inhibitors of renin: a review. Progress in Biochemical Pharmacology 12: 135-141, 1976
Raddatz P, Jonczyk A, Minck KO, Schmitges CJ, Sombroek J. Substrate analogue renin inhibitors containing replacements of histidine in P2 or isosteres of the amide bond between P3 and P2 sites. Journal of Medicinal Chemistry 34: 3267-3280, 1991
Repine JT, Kaltenbronn JS, Doherty AM, et al. Renin inhibitors containing alpha-heteroatom amino acids as P2 residues. Journal of Medicinal Chemistry 35: 1032-1042, 1992
Rosenberg SH, Kleinert HD, Stein HH, Martin DL, Chekal MA, et al. Design of a well-absorbed renin inhibitor. Journal of Medicinal Chemistry 34: 469-471, 1991
Shibasaki M, Asano M, Fukunaga Y, Usui T, Ichihara M, et al. Pharmacological properties of YM-21095, a potent and highly specific renin inhibitor. American Journal of Hypertension 4: 932-938, 1991
Skeggs JT, Lentz KE, Kahn JR, Hochstrasser H. Kinetics of the reaction of renin with nine synthetic peptide substrates. Journal of Experimental Medicine 128: 13-34, 1968
Stein HH, Fung AK, Cohen J, Baker WR, Rosenberg SH, et al. Slow, tight binding to human renin of some nonpeptidic renin inhibitors containing a 4-methoxymethoxypiperidinylamide at the P4 position. FEBS Letters 300: 301-304, 1992
Szelke M, Leckie BJ, Tree M, Brown A, Grant J, et al. H-77: a potent new renin inhibitor: in vitro and in vivo studies. Hypertension 4: 59-69, 1982
Thurston H, Swales JD. Action of angiotensin antagonists and antiserum upon the pressor response to renin: further evidence for the local generation of angiotensin II. Clinical Science and Molecular Medicine 46: 273-276, 1974
Timmermans PB, Carini DJ, Chiu AT, Duncia JV, Price Jr WA, et al. Nonpeptide angiotensin II receptor antagonists. American Journal of Hypertension 3: 599-604, 1990
Turker RK, Page IH, Bumpus FM. Antagonists of angiotensin II. In Page & Bumpus (Eds) Angiotensin. pp. 162-169, Springer Verlag, New York, 1974
Weber AE, Halgren TA, Doyle JJ, Lynch RJ, Siegl PK, et al. Design and synthesis of P2-P1'-linked macrocyclic human renin inhibitors. Journal of Medicinal Chemistry 34: 2692-2701, 1991
Wienen W, Mauz AB, Van Meel JC, Entzeroth M. Different types of receptor interaction of peptide and nonpeptide angiotensin II an-

tagonists revealed by receptor binding and functional studies. Molecular Pharmacology 41: 1081-1088, 1992
Williams GH, Hollenberg NK. Accentuated vascular and endocrine response to SQ20,881 in hypertension. New England Journal of Medicine 297: 194-201, 1977
Wong PC, Hart SD, Zaspel AM, et al. Functional studies of nonpeptide angiotensin II receptor subtype-specific ligands: DuP 753 (All-1) and PD123319 (All-2). Journal of Pharmacology and Experimental Therapeutics 255: 584-592, 1990a
Wong PC, Price WA, Chiu AT, Duncia JV, Carini DJ, et al. Nonpeptide angiotensin II receptor antagonists X: hypotensive action of DuP 753, an angiotensin II antagonist, in spontaneously hypertensive rats. Hypertension 15: 459-468, 1990b
Wong PC, Price WA, Chiu AT, et al. Nonpeptide angiotensin II receptor antagonists: studies with EXP9270 and DUP 753. Hypertension 15: 823-834, 1990c
Wong PC, Price WA, Chiu AT, et al. Nonpeptide angiotensin II receptor antagonists XI: pharmacology of EXP3174, an active metabolite of DUP 753, an orally active antihypertensive agent. Journal of Pharmacology and Therapeutics 255: 211-217, 1990d
Zusman RM. Renin- and nonrenin-mediated antihypertensive actions of converting enzyme inhibitors. Kidney International 29: 969-983, 1984
Zusman RM, Burton J, Christensen D, Nussberger J, Dodds A, et al. Hemodynamic effects of a competitive renin inhibitory peptide in humans: evidence for multiple mechanisms of action. Transactions of the Association of American Physicians 96: 365-374, 1983

Correspondence and reprints: Dr *Robert J. Cody*, Cardiology Division, The Ohio State University Medical Center, 601 Means Hall, 1654 Upham Drive, Columbus, OH 43210, USA.